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THE COBALT STORY.[1]

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I GREATLY appreciate the honour of being invited to deliver the Annie B. Cunning Lecture for 1958, and I am especially grateful for the suggestion that I relate something of the biological phenomena in which cobalt plays an essential part, for that subject is very near my heart.

This evening it is my intention to seek for a brief hour to beguile you from your more serious occupations by weaving together several sequences of observations, each sequence in itself a chapter of the story implied in the title allotted me, though each was apparently quite distinct until discovery of the important part played by cobalt in the nutrition of ruminants initiated investigations that brought together these strands into an uncommonly beautiful pattern, with cobalt the leitmotiv of its contexture.

[1] The eleventh Annie B. Cunning Lecture on Nutrition, delivered at a meeting of The Royal Australasian College of Physicians, Adelaide, July 18, 1958.

Thomas Addison (1793-1860).

On this occasion it is appropriate for the first strand to be essentially medical, and so as a beginning I am impelled to recall and pay homage to Thomas Addison, who was first to recognize pernicious anæmia as an entity and to describe the clinical symptoms of this peculiarly human malady. Addison was appointed assistant physician to Guy's Hospital in 1824, and soon became the spirit who provided an *élan* for the medical doings there that led to the professional and public esteem in which Guy's was then held, as it is now.

Even at the expense of a small digression, I should like to dwell a little on Addison's published works, because they illuminate the man, and even a cursory glance at them is enough to indicate the extent to which medical knowledge has progressed during the past century. Addison was certainly held in deep respect by his contemporaries; yet (I have it on the authority of his colleague Dr. Wilks[1]) in professional intercourse his peculiar disposition to bluntness of expression was misinterpreted by many as an assumption of haughty superiority—a common mistake being thus perpetuated

[1] In a biographical preface to the New Sydenham Society's "Collection of the Writings of the Late Thomas Addison, M.D., Physician to Guy's Hospital", edited by Dr. Wilks and Dr. Daldy, and published in 1868, eight years after Addison's death.

in estimating the character of a man whose energy of manner and resoluteness of expression were adopted, as they are more often than not, to cloak a covert physical nervousness.

Addison's mode of expression is, indeed, brisk and unqualified; so much so that now, when perusing his writings, one is easily led to overlook the great accessions to medical knowledge that have flowed as bounty from scientific research during the intervening 100 years. One reads, for instance, his vigorous disquisitions on "diseases of the lungs" with a feeling akin to frustration. Though they are impeccable clinical descriptions, they seem to miss entirely the essential point, until one realizes that they were written a third of a century before Robert Koch described to a small audience of 36 his discovery of the tubercle bacillus (1882), and many more years before this finding was accepted and its significance realized.

Addisonian Pernicious Anæmia.

Addison's descriptions of the syndrome styled by him idiopathic anæmia, which is the beginning of this strand of the cobalt story, and of the prostrating malady which he associated with abnormal pigmentation of the skin and showed was invariably accompanied by degenerative changes in the adrenal glands, are both contained in his brief treatise "On the Constitutional and Local Effects of Disease of the Supra-renal Capsules".[1] The former, for which he sought a pathological origin with no avail, is mentioned in the introduction of his paper virtually as an aside. To use his own words:

> It was whilst seeking in vain to throw some additional light upon this form of anæmia that I stumbled upon the curious facts that it is my more immediate object to make known to the profession . . .

The two quite distinct pathological entities which now bear his name, one, *Morbus addisonii*, typified by asthenia, and the other, Addisonian pernicious anæmia, typified by anæmia, were not clearly separated in this paper; in actual fact, immediately subsequent writers referred to them in the same sense. Nevertheless, masterly clinical descriptions of both were separately set out there.

Addison referred to pernicious anæmia in these words:

> For a long period I had from time to time met with a very remarkable form of general anæmia, occurring without any discoverable cause whatever — cases in which there had been no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease.
>
> Accordingly, in speaking of this form in clinical lecture, I perhaps with little propriety applied to it the term, *idiopathic*, to distinguish it from cases in which there existed more or less evidence of some of the usual causes or concomitants of the anæmic state.
>
> The disease presented in every instance the same general character, pursued a similar course, and, with scarcely a single exception, was followed, after a variable period, by the same fatal result.
>
> It occurs in both sexes generally, but not exclusively, beyond the middle period of life, and, so far as I at present know, chiefly in persons of a somewhat large and bulky frame, and with a strongly-marked tendency to the formation of fat.
>
> It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme. The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted; the pulse, perhaps, large, but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement; there is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth, and waxy appearance; the lips, gums, and tongue seem bloodless; the flabbiness of the solids increases; the appetite fails; extreme languor and faintness supervene, breathlessness and palpitations being produced by the most trifling exertion or emotion; some slight œdema is probably perceived about the ankles; the debility becomes extreme. The patient can no longer rise from his bed, the mind occasionally wanders, he falls into a prostrate and half-torpid state, and at length expires. Nevertheless, to the very last, and after a sickness of, perhaps, several months' duration, the bulkiness of the general frame and the obesity often present a most striking contrast to the failure and exhaustion observable in every other respect.
>
> With a single exception the disease, in my own experience, resisted all remedial efforts, and sooner or later terminated fatally.
>
> On examining the bodies of such patients after death I have failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences.

Fifteen years later, Samuel Fenwick, while assistant physician to the London Hospital, associated idiopathic anæmia with structural changes in the mucosa of the stomach.[1] During the course of discussing a case of anæmia, in which he found that the whole of the secreting structures of the stomach were atrophied, he remarked:

> Cases of fatal anæmia like the foregoing have probably fallen under the observation of most practitioners; at any rate, I can call to mind several in the course of my own experience. Dr. Addison evidently had such cases in his remembrance when he described "idiopathic anæmia". His brilliant discovery of the disease of the supra-renal capsules probably directed his attention from the condition and induced him to investigate only those cases in which the skin presented the peculiar discolouration. If, however, the general symptoms in the case described be compared with those present in Addison's disease they will be found to be remarkably similar . . . In both, irritability of the stomach is present . . . It is very desirable therefore that a careful microscopical examination of the stomach be made . . . At present we attribute to the supra-renal capsules an importance in the formation of the blood which the physiological facts at our command do not warrant: and perhaps future investigations may prove that the anæmia accompanying Addison's disease arises, not from any affection of these organs but from a coexisting atrophy of the stomach or other parts of the intestinal canal . . .

Thus he revealed the primary cause of the malady.

By the turn of the century the associated nervous disorder, in which the essential lesion is primary demyelination of the white matter of the spinal cord, was well established as an important part of the syndrome, and the somewhat inept but persistent name for it — "subacute combined degeneration" — was by then already in general use.

Advances in the art of hæmatology led to the recognition of the modification of bone-marrow function — the megaloblastic hyperplasia, and the lag in the rate of maturation of the red cells — which determines the blood dyscrasia. Precise descriptions were formulated of the hæmoglobinized erythroblasts, and of other abnormal, primitive, nucleated cells among the formed elements, which, together with prevailing macrocytosis and polychromasia, are so characteristic of the blood picture in Addisonian pernicious anæmia.

Thus by the end of the first quarter of this century the foundations had been laid for the great clarifications in the understanding of the ætiology of this fatal disease — namely, George Minot and W. P. Murphy's discovery of the curative properties of raw liver, and William Castle's brilliant demonstration that two factors are involved in maintaining the supply of hæmatopoietic principle essential for normal red cell production. These are an extrinsic factor, necessary for the maturation of red cells, which is present in some foods — liver being a potent source — and an intrinsic factor, present in normal gastric juice, which we now know is necessary for the absorption of extrinsic factor from the intestinal tract.

[1] Delivered to the South London Medical Society, and published in 1855 by S. Highley, London.

[1] Samuel Fenwick, "On Atrophy of the Stomach", *Lancet*, 1876, 2:78.

Before discussing the nature of the extrinsic factor, we might appropriately begin to spin a second strand, this time one made up of a sequence of events which, though quite distinct, contributed knowledge which led to an understanding of the nature of this accessory food factor.

Cobalt-Deficiency in Ruminants.

A lore, hard-born of experience reaching back to early historical times, warns the grazier of a wasting malady which affects flocks and herds depastured continually on certain tracts, and exhorts an occasional change to curative areas. For centuries shepherds have had their own descriptive terms for this marasmus; in the British Isles, the words "pining", which is early Anglo-Saxon, "vinquish", which is ancient Scottish, and "daising", which possibly stems from old Scandinavian roots, still persist in local dialects of small isolated communities living in the vicinity of areas on which sheep and cattle have long been known to waste and die if grazed without change. Elsewhere, "bush sickness" (New Zealand), "nakuruitis" (Kenya), "enzootic marasmus" (Western Australia), etc., describe this syndrome, and here in South Australia early settlers soon encountered a closely similar malady, which they called "coast disease",[1] because of its association with the sea shores. Sheep and cattle confined to the calcareous littoral dunes were observed invariably to become ill and lethargic, and soon declined and died if left there without occasional change to the healthier but sometimes poorer grazings of the hinterland. Horses and, apparently, the native marsupial fauna suffer no untoward effects, and the introduced European rabbit, a coprophagus beast, thrives and, if unchecked, multiplies to plague dimensions on the heavily grassed cover of particularly affected calcareous dunes.

This wasting malady is encountered in most countries where animal industry is fostered. It prevails on areas which share neither obvious geochemical similarity nor common geographical features; on a diversity of terrain, widely dispersed, on soils as little alike as, for instance, those derived from acidic volcanic magmas, over which bush sickness occurs in New Zealand, and those derived from the calcareous, post-Pliocene, æolean sands, over which coast disease occurs in southern Australia.

At this stage, even at the expense of becoming tedious, I suggest that we might appropriately take passing notice of the symptoms that characterize coast disease, for many of the clinical features recognized by close study of this malady are common to those of the wasting syndrome as it is observed elsewhere, and some are reminiscent of Addisonian pernicious anæmia. Briefly, the syndrome is that of a progressive wasting disease, in which a failure of appetite and profound anæmia are prominent features. A sheep in an advanced stage of the malady is emaciated and lethargic; it presents a demeanour of dull, rheumy-eyed listlessness; its buccal and conjunctival mucosæ are blanched, and its skin is pale and fragile. The blood volume and the concentration of protein in the plasma become materially reduced, and the oxygen-carrying capacity often falls to 30% of normal or even lower, according to the state of deficiency. When profound, the anæmia is almost invariably macrocytic, with marked poikilocytosis, and with signs suggestive of a serious retardation of the rate of maturation of the red cells—polychromasia and punctate basophilia prevail—and abnormal, primitive, nucleated erythroblasts circulating among the formed elements within the blood-stream proclaim a functional disorder of the bone marrow. In the most severe form of the malady, appetite fails progressively until the animal succumbs to a state of inanition. Even then autopsy reveals no gross changes; in sheep in which the disease has advanced to the terminal stages the condition of the viscera is that of the hunger œdema which supervenes on prolonged semi-starvation. There are no nervous sequelæ.

These are extreme consequences suffered by animals confined to particularly affected areas; the deficiency state most often encountered is a milder form, in which the condition is one of poor health rather than of frank disease.

In 1931, when we began our series of experimental studies, the ætiology of this malady was quite obscure. The possibilities of zymotic, viral or parasitic origin were remote in a disease confined within the bounds of particular areas that often are quite sharply delineated from healthy terrain, and so a guiding hypothesis that the fodder plants available on the affected areas lacked a nutrient element essential for the sustenance of ruminants was inescapable. We observed from therapeutic tests that sheep in an advanced stage of the malady responded dramatically to dosing with mixtures of soluble salts of the heavy metals (nickel, cobalt, molybdenum, copper, zinc, etc.) found consistently to be present as traces in living tissues, and so began a series of well-controlled experiments with flocks confined to the seriously affected littoral. Responses were so spectacular that the planning of experiments to identify the active constituents was a matter of simple logic. At this early stage, Waltner's discovery that cobalt, administered either orally or parenterally, induced marked polycythæmia in the rat, influenced us to concentrate our attention somewhat more especially upon the effect of cobalt than perhaps was then justified, and so led us more directly to the proof that the wasting syndrome of grazing stock resulted from a lack of sufficient cobalt in the fodder of the affected areas. It is now obvious that the phenomenon observed by Waltner had nothing in common with the malady we are studying—the polycythæmia induced by cobalt in normal animals is the result of a passive physiological compensation to partial anoxia, due possibly to combination with functional thiol (–SH) groups within the tissues.

Unequivocal demonstrations that small supplements of soluble cobalt salts, administered *per os*, will prevent the untoward symptoms which invariably appear in sheep confined to the calcareous littoral tracts, and also rapidly restore normal health to animals that have developed this wasting syndrome, indicated strongly that cobalt was an essential micronutrient element, and within a remarkably short time the similar maladies that affect stock elsewhere were all proved to respond to cobalt. The first was enzootic marasmus in Western Australia, where investigators were seeking the potent element by fractionating a crude, hydrated iron ore, limonite, which they had observed to elicit a curative response when administered in massive amounts to stock that had developed "Denmark disease" after grazing for a period on affected areas. The next was the bush sickness of New Zealand, where investigators were seeking the active constituent in extracts prepared from the soils of areas known to be healthy. Then, by direct experimental tests, salt sickness of Florida, pine of the Cheviots, and daising and vinquish in other parts of Scotland, pining disease of Devon, Cornwall, Herefordshire and Worcestershire in England, and nakuruitis of Kenya, in East Africa, were all shown to respond in a like manner to cobalt. The untoward effects of cobalt deficiency have since been recognized in stall-fed ruminants and in flocks and herds grazing certain areas in U.S.A., in Canada, in the Hebrides, in Ireland, in Norway, in Sweden, in Denmark and in Estonia, and no doubt they prevail in many other areas.

The quantity of cobalt necessary to fulfil the nutritional requirements of ruminants is certainly very small; the dose, equivalent to 1 mg. of cobalt per day, arbitrarily adopted in our first experiments with sheep on very deficient pastures, was in considerable excess of the requirement; one-twentieth of this amount proved enough in later critical experiments. To fulfil continually the physiological requirements of sheep, and almost certainly of cattle, the fodder must contain in excess of 0·08 μg. of cobalt per gramme, dry weight.

[1] Coast disease is actually the result of a deficiency of both cobalt and copper; the untoward effects of the latter are usually masked by the more rapidly fatal consequences of the former. Where the dual deficiency prevails, appropriate treatment of the grazing animal with cobalt or with copper will reveal the uncomplicated syndrome of either deficiency. Copper deficiency manifests itself first of all by profound changes in the wool-fleece, and later, by a microcytic hyperchromic anæmia.

Our early demonstration that, to be effective, cobalt must be ingested—when injected into the blood-stream cobalt proved to be quite inactive as a specific for the wasting syndrome—indicated that its primary action was exerted within the alimentary canal, probably upon the rumen flora. The proof that the rumen flora is an essential link in the functional activity of cobalt in the metabolism of ruminants came later.

Animal-Protein Factor.

A third strand may be spun from a sequence of studies initiated when animal industry became aware that plant-protein concentrates could not effectively replace animal-protein concentrates in rations for poultry and pigs.

Experience of many years of feeding practice had implied that the quality of vegetable proteins was very inferior to that of animal proteins. In general, however, the differences were tacitly assumed to be due to the known differences in the relative proportions of the essential amino acids in the two sources of proteins, and so the matter was not investigated intensively until the large-scale adoption of soy-bean meal as a substitute for animal-protein concentrates in poultry rations made it clear that poultry could not be supported on all-plant rations under prevailing conditions of husbandry.

Mature hens, confined to rations comprised solely of plant products, suffer no immediate impairment of health, nor is their egg-laying capacity particularly affected, at least for a considerable period. The hatchability of their eggs, however, is reduced very materially by the death of many of the embryos a few days prior to full-term incubation, and the comparatively few chicks that do hatch and survive grow poorly and mature abnormally slowly. Experimental investigations which sought a reason for this soon revealed that a hitherto unknown accessory food factor was involved, and that this animal-protein factor was absent from foods of vegetable origin and from yeast, but present in meat-meal, fish-meal, etc., liver and protein-free liver extracts being particularly rich sources. An observation that the barnyard fowl, by supplementing its all-plant rations with the odd undigested grain scratched from the midden, remained vigorously healthy, led to the proof that cow-dung contained a very considerable quantity of this essential nutrient, and to the realization that interpretations of many of the earlier experiments had been confused by complications introduced by coprophagy, for it soon became obvious that fæces of all animals were potent sources of this vitamin. Thus a suspicion that this growth factor was a product of the metabolic activity of microflora within the intestinal tract grew apace.

The Isolation and Chemical Structure of the Cobalt-Containing Accessory Food Factor, Vitamin B_{12}.

The fourth strand, essentially a chemical extension of the first, revealed the relationship of all the preceding three, and set the pattern.

It began in 1948, with the isolation from liver, in crystalline form, of the anti-pernicious anæmia factor (Castle's extrinsic factor) independently by Dr. Ernest Lester Smith and his colleagues in England, and by Dr. Karl Folkers and his colleagues in the United States. The former group depended upon clinical tests as a guide to purification procedures, and the latter upon a microbiological assay, the responsive organism being a strain of *Lactobacillus lactis* for which the active constituent is an essential growth-factor.

The deep red, beautifully crystalline principle proved to be a large molecule in which an atom of cobalt is firmly coordinated; the molecular weight is close to 1500, and the cobalt content about 4·5%.

This complex was named vitamin B_{12} by Folkers, "because the name has not yet been used in the B series and connotes only nutritional significance". That it is, surely, the anti-pernicious anæmia factor was indicated by the observation that 3μg. of it produced an easily recognizable positive reticulocyte response when introduced parenterally into a patient suffering a relapse of Addisonian pernicious anæmia. Almost immediately after its isolation, vitamin B_{12} was shown to be identical with animal protein factor; and it soon became apparent that the basic reason for the essential requirement of a modicum of cobalt in the fodder of ruminants was to ensure the synthesis of vitamin B_{12} by the rumen flora, in sufficient amount to meet what we have since proved to be the relatively large demands of these animals for this accessory food factor. The three widely different strands were thus brought together.

Before we consider the physiological functions of vitamin B_{12}, it would be proper to consider its chemical structure, and to pay tribute to the fine work that has been devoted to its elucidation.

The unique and striking physiological properties of this crystalline biological product immediately awakened the interest of chemists, with the result that its structure is now known, and that we know more about the detailed stereochemical distribution of its component atoms than we know about many much simpler compounds; the whole armoury of the modern weapons of chemical research was brought to bear on it.

Classical degradation methods, aided by partition chromatography, revealed that a nucleotide-like structure, 5:6-dimethyl-1-(alpha-D-ribofuranosyl)-benziminazole 3'-phosphate, is attached through the nitrogen in position 3 on the benziminazole residue to an atom of cobalt coordinated in the centre of the greater, crystallographically planar, relatively more stable part of the molecule, which, because of its resistance to fragmenation by the usual chemical means, defied interpretation for a time. However, as alkali-fusion products of vitamin B_{12} gave reactions characteristic of certain cyclic five-membered nitrogen-containing compounds, there was an early suspicion that this more stable part of the molecule was a porphyrin.

A molecule of Dg-1-amino-2-propanol, linking the phosphate of the nucleotide with the main part of the molecule, was isolated among the products of mild acid hydrolysis, and a labile cyanogen group, attached to the cobalt atom, was demonstrated early in the studies. This latter group exchanges readily with hydroxyl and other groups, and may later prove to be the active centre of the enzyme pattern in which vitamin B_{12} undoubtedly plays a part.

The structure of the molecule, and especially of its cobalt-containing part, was most elegantly solved by a group of crystallographers working in close collaboration at Oxford and at Princeton under the leadership of Dr. Dorothy Crowfoot Hodgkin. Complete three-dimensional X-ray data were obtained from each of four crystals, one of dry vitamin B_{12}, one wet in equilibrium with its mother liquor, one in which the cyanogen was replaced by selenocyanide to provide another reference point, and one of the red degradation product, now called corphinic acid, that was isolated by Sir Alexander Todd and his colleagues at Cambridge.

After the positions of the heavy atoms had been identified by the application of Patterson methods, the immense task of computation implied in the three-dimensional Fourier analysis of the diffraction data was undertaken to obtain an approximation to the correct electron density series that correspond to actual atomic positions within the molecule.

The outline of the nucleotide was recognized by this means between the cobalt and the second moderately heavy peak resulting from the phosphorus atom, and surrounding the cobalt atom a group of almost planar form, similar in dimensions to a porphyrin nucleus, was located.

More detailed series of calculations suggested that, in fact, no true porphyrin structure was present in the molecule—three of the five-membered rings appeared each to be separated by a single atom that would correspond to the methene links in the porphyrins, but the fourth seemed directly bonded to the first. This surprising and quite unique atomic arrangement was confirmed by a similar examination of the cobalt-containing hexacarboxylic acid (corphinic acid) that results from mild alkaline hydrolysis of vitamin B_{12}. In this, the relative dispositions of atoms

within the planar group were found to be unchanged and essentially in the same pattern.

Further studies, made feasible by electronic computing machines, located most of the atoms of the side groups other than those of hydrogen, and, when these were combined with the chemical findings, the structure of the molecule was revealed. Of the crystallographic approach—essentially, the computation of relative electron density distributions from the amplitudes and phases of the X-ray reflexions from crystals—which so elegantly showed the intimate structure of vitamin B_{12}, Dr. Dorothy Crowfoot Hodgkin remarked:

> The process by which we have found the atomic distribution is in no sense automatic or fool-proof. Indeed, our best evidence that our process works at all is the extraordinarily reasonable and coherent molecular structure it has given for this vitamin.

Incidentally, the four heterocyclic components of the cobalt-containing moiety are not true pyrrole rings, as each contains at least one tetra-substituted beta-carbon atom. However, the fact that the acetic and propionic acid side chains attached to these heterocyclic rings are disposed in the same pattern as they are on the pyrrol components of the uroporphyrin molecule suggests that vitamin B_{12} and the porphyrins have essentially a common origin.

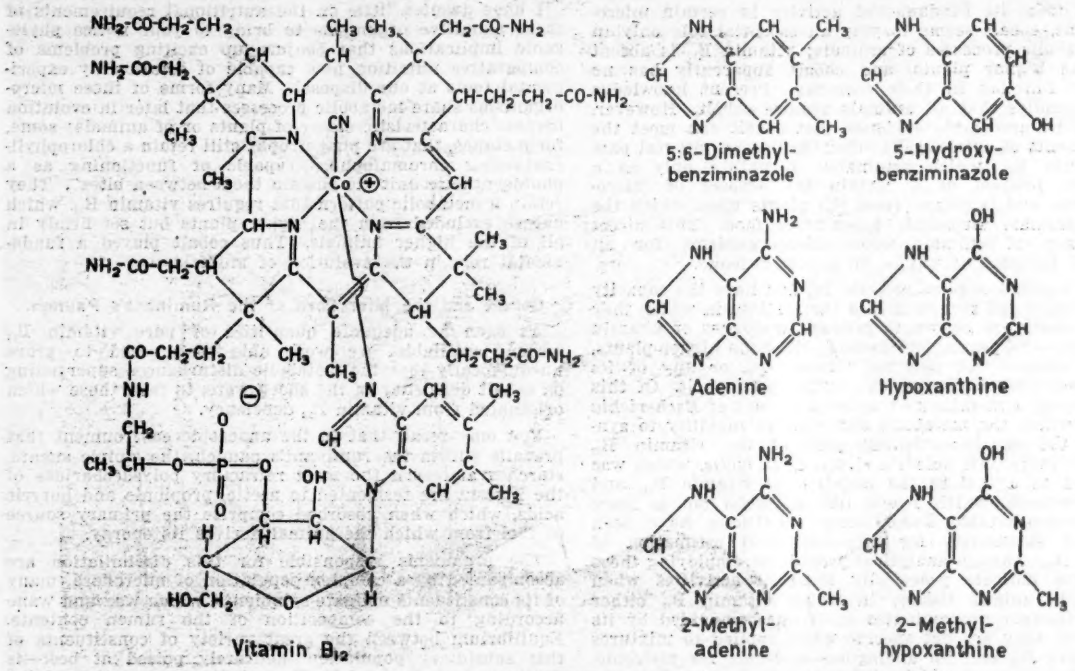

FIGURE I.

The above structure of vitamin B_{12} has been revealed by researches of several groups of organic chemists (for literature, refer to E. Lester Smith and K. Folkers *et alii*, pages 1 to 9 and 9 to 31, respectively, in *"Vitamin B_{12} und Intrinsic Factor"*, Stuttgart, 1957) and by X-ray crystallographic studies mentioned in the legend of Figure II. In the large vitamin B_{12} molecule, a nucleotide, 5:6-dimethyl-1-(alpha-D-ribofuranosyl)-benziminazole 3'-phosphate, is linked via its phosphate through isopropanolamine to the (f) propionyl group on C atom 17 in the D ring of the substituted, porphyrin-like corphyrinic amide nucleus, and is bonded, via the (3) N of the benziminazole residue to the cobalt atom, held within this nucleus. The vitamin, which is the essential nutrient for animals, differs from its naturally occurring analogues usually in the structure of the nitrogenous base of the nucleotide. Thus the place of 5:6-dimethyl-benziminazole present in vitamin B_{12} is taken, by 5-hydroxy-benziminazole in Factor III, by adenine (6 amino-purine) in pseudo-vitamin B_{12}, by hypoxanthine in Factor G, by 2-methyl-adenine in Factor A, and by 2-methyl-hypoxanthine in Factor H, etc.

Cobalt-Containing Analogues of Vitamin B_{12}

Fifty years before the discovery of vitamin B_{12} the fact that cobalt was an essential nutrient element for the growth of *Aspergillus niger* was demonstrated, and hints arising from more recent observations directed attention to the possibility that vitamin B_{12} might have a bacterial origin. Just prior to the isolation of vitamin B_{12} from liver, Folkers and his colleagues separated an identical product from the fermentation liquors of *Streptomyces griseus*. This abundant source of the vitamin rendered possible the great volume of research activity in the biological, chemical and clinical fields that has so greatly illuminated its nature and function.

Isolation of vitamin B_{12} was greatly facilitated by its intense red colour, for in the latter stages of purification, when the active principle was being eluted from suitably prepared chromatographic columns, all that was necessary was a close observation of the progress of the red bands. The cobalt-containing, porphyrin-like part of the molecule, corphinamide, was separated in this way from the products of mild perchloric acid hydrolysis of vitamin B_{12}, a process which removes the nucleotide with little damage to the rest of the molecule. The resulting red-coloured complex proved to be identical with Factor B, previously isolated from cow-dung.

Application of the methods utilized for the separation of vitamin B_{12} to the contents of the fore-stomachs and lower levels of the intestinal tracts of ruminants, and to the excreta of other animals, resulted in the separation of several analogues in which cyanocorphinic acid (or its hexa amide) is almost certainly a common nucleus. These factors, designated, pseudo-vitamin B_{12}, Factor A, Factor B, etc., are all of bacterial origin. Apart from Factor B, which is a 2CN derivative of cyano-corphinamide—i.e., essentially vitamin B_{12} devoid only of its nucleotide—those that have been crystallized and chemically identified differ from the vitamin B_{12} molecule chiefly in the nature of the nitrogenous base of the nucleotide. The 5:6-dimethyl-benziminazole in the nucleotide of the vitamin B_{12} molecule is replaced in Factor III by 5-hydroxy-benziminazole, in

pseudo-vitamin B_{12} by adenine (6-amino-purine), in Factor A by 2-methyl-adenine, in Factor G by hypoxanthine (6-hydroxy-purine), and in Factor H by 2-methyl-hypoxanthine. At the present time over a dozen naturally occurring analogues have been described, each differing very manifestly in its capacity to promote the growth of organisms employed for microbiological assay.

The Microbiological Origin of Vitamin B_{12} and its Phylogenic Implications.

Apart from its fundamental activity in certain microorganisms, cobalt seems to play an essential role only in the metabolic processes of animals; vitamin B_{12} is absent from the higher plants, and cobalt apparently has no essential function in their economy. Present knowledge clearly implies that all animals require cobalt. However, there is no acceptable evidence that cobalt can meet the requirements of animal cells other than as an integral part of vitamin B_{12}, which originates in nature only as a metabolic product of a certain few classes of microorganisms, and is absent from the plants upon which the higher animals ultimately depend for food. This direct dependence of animals upon microorganisms for an essential foodstuff is unique in our knowledge.

Many bacteria require vitamin B_{12} and have the capacity to synthesize and secrete it into the medium in which they grow. Others are known to produce analogues of vitamin B_{12}. Some—the yeasts, for instance—like the higher plants, neither require nor produce vitamin B_{12} or any of its analogues. Others require but cannot produce it. Of this latter group, a methionine-requiring mutant of *Escherichia coli*, in which the metabolic defect is an inability to synthesize the cobalt-containing part of the vitamin B_{12} molecule (corphinic acid), a strain of *L. lactis*, which was employed as a tool in the isolation of vitamin B_{12}, and *L. leichmannii*, which reacts like *L. lactis* but is more stable and tractable under assay conditions, have been employed extensively for microbiological estimation of vitamin B_{12}. Though analytical procedures employing these organisms indicate practically identical activities when applied to animal tissues in which vitamin B_{12} either overwhelmingly predominates or is unaccompanied by its analogues, they are not specific when applied to mixtures of vitamin B_{12} and its analogues—molecule for molecule, the analogues exert widely different stimulating effects on them under assay conditions.

The Euglenoidæ are more specific in their demands. This abundant tribe of phytoflagellates lies in the rather dim regions of phylogeny where plants and animals begin to emerge from a common stock. It embraces a company derived from green-pigmented stock in which a single mutation can induce the loss of chlorophyll. The diverse forms allotted to it by cautious taxonomists, hesitant to affiliate them with any other algal group, range from green species capable of supporting themselves by photosynthesis, to colourless phagotrophs which, like animals, ingest particulate food.

Strains of *Euglena gracilis* var. *bacillaris*, a member of this group, have been employed extensively with varying success as a tool for the estimation of vitamin B_{12}. Neither methionine nor deoxyribosides can replace the demands of these organisms for vitamin B_{12}, though certain analogues —Factor A and pseudo-vitamin B_{12}, for example—will fulfil this requirement.

The capacity of Euglenids to concentrate and utilize vitamin B_{12} from dilute solutions is outstandingly efficient. When the supply is limiting, these organisms are extremely sensitive to changes in the concentration of vitamin B_{12}—so much so that additions of one part of vitamin B_{12} to a million million parts of culture medium (i.e., 1 $\mu\mu$g. of vitamin B_{12} per millilitre) have been stated to elicit measurable increments in their growth rate.

The Chrysomonads, derived from brown-pigmented stock and assigned with more confidence by taxonomists to a phylogenic setting more immediately precursor of the Protozoa, are, like the higher animals, very exacting indeed in their demands for vitamin B_{12}. *Ochromonas malhamensis*, a member of this family that has been isolated and supported in pure culture, is both phagotrophic and photosynthetic. It demands vitamin B_{12} *per se*. Its requirements for vitamin B_{12} cannot be met by any naturally occurring analogues, other than by relatively large quantities of Factor I (vitamin B_{12} III), which differs only in a very minor respect from vitamin B_{12} (the base of the nucleotide in it is 5-hydroxy-benziminazole instead of 5:6-dimethyl-benziminazole), and which has a similar capacity to provide the vitamin B_{12} requirements of birds and mammals.

I have dwelt a little on the nutritional requirements of these primitive organisms to bring to your notice phylogenic implications that conjure up exciting problems of comparative nutrition now capable of solution by experimental tools at our disposal. Many forms of these microorganisms share metabolic processes that later in evolution became characteristic either of plants or of animals; some, for instance, that are phagotrophs still retain a chlorophyll-containing chromatophore capable of functioning as a photosynthetic unit "to sustain them between bites". They retain a metabolic pattern that requires vitamin B_{12}, which nature excluded from the higher plants but set firmly in all of the higher animals. Thus cobalt played a fundamental role in the evolution of animals.

Cobalt and the Microflora of the Ruminant's Paunch.

As soon as adequate quantities of pure vitamin B_{12} became available, we were able to proceed to prove unequivocally that the metabolic disturbances supervening on cobalt deficiency in the sheep were, in fact, those which originated from vitamin B_{12} deficiency.

You may recall that in the anaerobic environment that prevails within the ruminant's paunch, the simple sugars, starches and even the most refractory polysaccharides of the ingesta are fermented to acetic, propionic and butyric acids, which when absorbed comprise the primary source of fuel from which the animal derives its energy.

The organisms responsible for this dissimilation are accompanied by a complex population of microflora, many of its constituents obligate symbionts, which wax and wane according to the composition of the rumen contents. Equilibrium between the great variety of constituents of this subsidiary population—delicately poised at best—is particularly influenced by the cobalt concentration of the rumen contents. When the cobalt available there is reduced to a concentration that cannot provide the needs of the organisms which require this element, very manifest changes in the nature of the rumen-flora supervene, without material change in the overall number of microorganisms, which in the rumen contents of our experimental animals is usually of the order of 10^{10} per gramme, irrespective of the cobalt concentration. The change following withdrawal of a cobalt supplement from an experimental sheep that has for some time subsisted on a fixed cobalt-deficient ration (comprised of fodder containing less than 0·03μg. of cobalt per gramme) is dramatic. During the five days subsequent to the last supplement, the cobalt concentration within the rumen contents falls exponentially to the low level determined by the deficient ration. The concentration becomes limiting when it falls below five parts of cobalt in 10^{10} of solution, at which stage certain classes of microorganisms, normally present in relatively small numbers, become better able to compete, and with this advantage multiply and overwhelmingly dominate the population. On reinstatement of the cobalt supplement, the reverse procession takes place to establish the normally prevailing dynamic equilibrium between the constituent classes of the microbial population.

Dilution below the limiting cobalt concentration is accompanied by a relatively precipitate decrease in the rate of vitamin B_{12} synthesis; for instance, under our experimental conditions the 600 to 1000 μg. of vitamin B_{12} per day produced when the cobalt supplement is provided falls, in the course of the five days after removal of the supplement, to between 40 and 50 μg. per day, and production stays at this level so long as the low intake of cobalt remains unaltered.

These very striking changes exert no apparent effect on the constituents of the rumen microflora that function in the fermentation of carbohydrates. Cobalt, seemingly, does not enter into their economy. Certainly their activity is not diminished in any obvious way by the low concentrations that prevail in the rumen of sheep confined to fodders that are very short of cobalt. Irrespective of the cobalt concentration, the carbohydrates are fermented at the same rate, with the production of the same proportions of acetic, propionic, and butyric acids; the overall digestibility of the ration is unaltered, and provided that the animal itself is not short of vitamin B_{12}, the use it makes of the combustible energy in the products absorbed from its intestinal tract remains unchanged within the small experimental error involved in metabolic studies.

As the physiological status of sheep on frankly cobalt-deficient rations may be maintained indefinitely simply by parenteral injection of appropriate quantities of vitamin B_{12}, it is clear that the marked influence of cobalt deficiency on the nature of the mixed population of microorganisms within the rumen has little influence on the nutritional well-being of the animal itself, other than to reduce the supply of the essential accessory food factor, vitamin B_{12}, and possibly also the supply of folic acid. However, the very striking change in the metabolic propensities of the microbial population which is brought about may, in certain circumstances, become of great importance to the animal.

Vitamin B_{12} Metabolism in the Sheep.

Our experimental determinations of the rate of biological turnover of vitamin B_{12} in the tissues of the sheep indicate that close to 7·5 μg. of vitamin B_{12} are irretrievably lost each day in the course of normal metabolism, and so this amount must be made good if a physiological state is to be maintained. The efficiency of absorption of vitamin B_{12} by ruminants is very poor indeed; little more than 3% of that produced in the rumen of sheep finds its way into the blood-stream, though the greater part is liberated from the microorganisms when they are subjected to the conditions which prevail in the abomasum. If, then, sufficient of the vitamin is to become available to provide for normal physiological function within the tissues, relatively massive amounts (more than 200μg. of vitamin B_{12} per day) must traverse the levels of the intestinal tract where absorption is effected. The normally very poor capacity of ruminants to absorb vitamin B_{12} is, in effect, closely parallel to the pathological condition imposed by the gastric defect that leads in human subjects to pernicious anæmia.

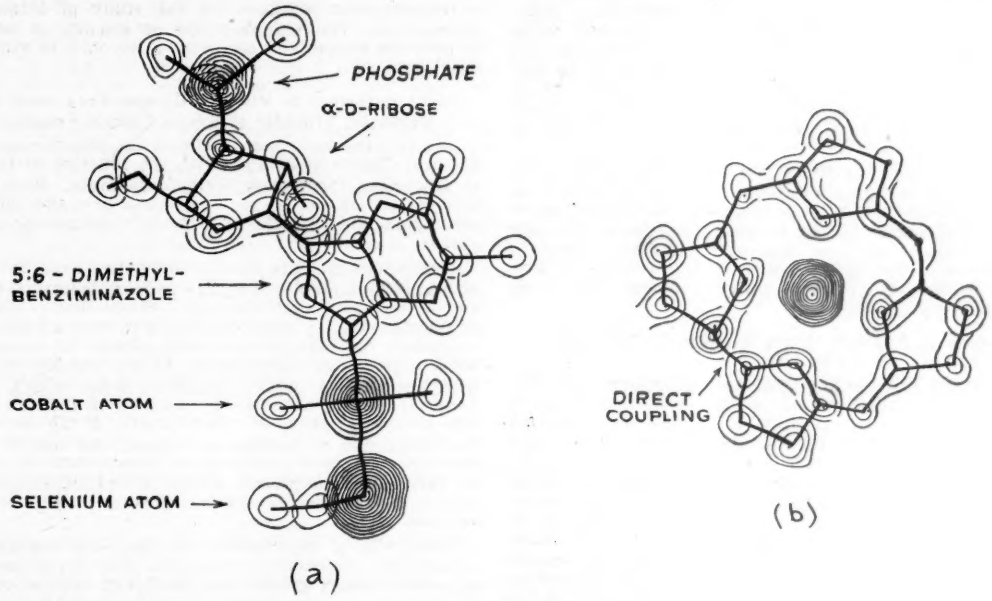

FIGURE II.

Positions of certain atoms in vitamin B_{12}–SeCN as derived by Dorothy Crowfoot Hodgkin et alii (Nature, 1954, 174: 1170) from calculated three-dimensional electron density distributions. (a) Density peaks corresponding to phosphate, ribose, benziminazole, cobalt and seleno-cyanide viewed along the b-axis. The seleno-cyanide was employed to provide another relatively dense reference point. (b) The pseudo-porphyrin nucleus (now called the corrin ring) was revealed unequivocally and for the first time by the above contour section which views, along the a-axis, the 3-d electron density distributions of the "planar" group of vitamin B_{12} (Hodgkin et alii, ibidem). This structure lacks one of the four methene (–CH_2–) groups which link the four constituent pyrrol groups in the macro-ring of the porphyrins. In the corrin ring, two of the four pyrrol rings are directly coupled.

However, when the cobalt in the fodder imposes no limit, sufficient vitamin B_{12} is produced (600 to 1000 μg. per day) in the rumen of sheep to ensure absorption of more than enough to provide for the immediate requirements imposed by biological turnover and excretion. The excess is laid down in the tissues, mainly in the liver. The livers of adult sheep grazed on areas where adequate cobalt is available usually contain more than 1·5 mg. of vitamin B_{12} (i.e., between 1·3 and 2·0 μg. per gramme). This reserve is drawn upon in periods when cobalt shortage within the fodder reduces production to levels no longer sufficient to maintain nutritional equilibrium, and thus the animal is able to withstand seasonal shortages provided they are not unduly protracted. Under very serious conditions of cobalt shortage in the fodder, an adult sheep suffers a net loss of close to 6 μg. of vitamin B_{12} per day, and so, provided that it has a normal store in its liver at the beginning, it will suffer no untoward effects for upwards of a year after transfer to the deficient grazing.

Symptoms of the deficiency appear when the concentration of vitamin B_{12} in the liver is reduced below 0·1 μg. per gramme, wet weight, at which stage of depletion the capacity of a channel of intermediary metabolism in which the vitamin is a functional unit becomes so restricted as no longer to allow the clearance of the metabolites arising

from a normal full feed. Appetite begins to fail, and subsequently food intake decreases progressively as the vitamin B_{12} status worsens; the animal loses weight steadily until it dies of inanition, evincing no special abnormality other than a macrocytic anæmia which, although frequently profound, is certainly subsidiary to the main metabolic lesion.

The Anæmia Supervening on Cobalt Deficiency in Ruminants.

Anæmia is not an invariable symptom of vitamin B_{12} deficiency in ruminants. In many of our experimental sheep, kept under carefully controlled laboratory conditions and fed on rations very short of cobalt, the deficiency syndrome has progressed to the terminal stages without intervention of any serious degree of anæmia. However, when anæmia does develop, the oxygen-carrying capacity of the blood usually falls in the course of several weeks to less than 30% of normal, and the blood picture then proclaims a disorder of the bone marrow very similar to that which is evident in pernicious anæmia, and like the latter, it responds dramatically to treatment with folic acid.

The human and the ovine syndromes of vitamin B_{12} deficiency have certain similarities; in both the anæmia is resolved by folic acid, but the basic metabolic disturbance remains unaffected. In the former, the malady proceeds to the terminal nervous disorder, subacute combined degeneration of the spinal cord; in the latter, the progressive failure of appetite is unimpeded and death from inanition ensues.

Failure of Appetite in the Vitamin B_{12}-Deficient Ruminant.

This failure of appetite, the most prominent and certainly the most basic feature of the ovine syndrome of vitamin B_{12} deficiency, reflecting as it does with amazing precision the extent of the metabolic lesion, is not particularly evident in the human syndrome of vitamin B_{12} deficiency. One is led to suspect that the appetite centre is depressed by an increased concentration of one or other of the fatty acids in the circulation, or possibly by an accumulation of an intermediary product of their metabolism stemmed back by the animal's reduced capacity to deal with fatty acids. The direct cause of this depressing effect is not yet clear. Whatever the chain of events responsible, the intake of fodder is restrained by it to quantities that may be cleared through the restricted metabolic channel at a rate sufficient to prevent very serious accumulation of intermediary products within the tissues.

The Primary Metabolic Lesion Imposed in Ruminants by Vitamin B_{12} Deficiency.

I shall not attempt to discuss here our current experimental investigations, which are seeking to locate more precisely the metabolic lesion. I shall merely mention that the defect of intermediary metabolism brought about by vitamin B_{12} deficiency in ruminants is in the chain of processes which deal with simple fatty acids, a chain of events which is of prime importance to animals that derive practically the whole of their energy requirements from acetic, propionic and butyric acids.

Our studies of the relative rates at which the simple fatty acids are utilized respectively by carefully pair-fed normal and frankly vitamin B_{12}-deficient sheep have revealed two types of metabolic disturbances associated with the deficiency state: one in which the rates of metabolism of propionic acid, of acetic acid and of glucose are all markedly depressed, and in which the rise in blood sugar level that normally follows intravenous injection of propionate is absent; and one in which only the rate of metabolism of propionate is retarded and a transient rise in blood sugar level supervenes on injection of propionate, as it does in normal animals. The former condition reverts to the latter after parenteral injection of generous amounts of folic acid into the affected animal. Such a phenomenon might be expected if a coenzyme was limiting an alternative pathway of metabolism.

I should like to dwell on this aspect of the problem, for it embraces the core of the subject; but the investigations are in progress, and the nature of the biochemical mechanisms which become impaired is not yet sufficiently understood to justify a clarification which may be of interest to this meeting; the subject is still one for specialists.

One may now say with confidence, however, that all findings from our physiological experiments *in vivo* with intact, vitamin B_{12}-deficient sheep, and from our biochemical studies *in vitro* with tissue preparations from their livers, imply that vitamin B_{12} serves metabolic pathways (i.e. those involved in the metabolism of propionic acid) which are of vital importance to the ruminant, but which are not of such great moment in human tissues or in the tissues of the laboratory animals usually employed as experimental subjects for the study of intermediary metabolism. The manifestation of anæmia is subsidiary in both the human and the ovine syndromes of vitamin B_{12} deficiency.

The Implication of Vitamin B_{12} and Folic Acid in the Metabolic Transfer of Single Carbon Fragments.

Many studies have indicated that the function of vitamin B_{12} is so closely associated with the function of folic acid as to render the two difficult to separate. Both express their activities in the metabolic channels that effect the production and transfer of fragments containing a single carbon atom.

Such fragments are known to be transferred in living processes as methyl ($-CH_3$), as hydroxy-methyl ($-CH_2OH$), and as formyl ($-CHO$) groups. Production of the amino acid methionine by transfer of methyl from a methyl donor —choline, for example—to homocysteine, is characteristic of the first; the methylation of the nucleotide, deoxyuridylic acid, to deoxy-thymidylic acid, which possibly proceeds through a 5-hydroxy methyl substitution, would, if this course is taken, be characteristic of the second; and the utilization of formate as a source of the C2 and C8 atoms of the purine molecule is characteristic of the third of these three oxidation levels, at which single carbon atoms are known to be transferred in the tissues of animals.

Consensus of experimental findings has suggested that vitamin B_{12} is involved more especially in the production of active methyl groups, and that folic acid or one of its derivatives merely functions as the transferring agent. This general hypothesis no longer fits the observations. The recent experiments of Dr. Donald Woods and his colleagues at Oxford have shed a different light on the problem, for the findings, as the authors mildly remark, "are compatible with a view that vitamin B_{12} has a function in the transfer of the hydroxy methyl group to homocysteine or in its final reduction to a methyl group". Extracts were made by treating, with ultrasonic vibration, suspensions of the mutant strain of *E. coli*, which, you may recall from our previous considerations, lacks in the absence of added vitamin B_{12} the ability to methylate the thiol ($-SH$) group of homocysteine to produce the amino acid methionine essential for its growth. In these extracts, synthesis of methionine from homocysteine and serine was increased about fourfold by the addition of vitamin B_{12}. The addition of the coenzyme form of folic acid (tetrahydro-pteroyl-glutamic acid) was necessary for optimum synthesis, and if the complex formed by treating this coenzyme with equimolar quantities of formaldehyde was added, the reaction proceeded in the absence of the donor, serine, vitamin B_{12} still being essential. When added in concentrations up to 7×10^{-9} molar, vitamin B_{12} increased the rate of formation of methionine sixfold to eightfold. Clearly, this field is beginning at last to promise satisfactory harvest.

Vitamin B_{12} and Addisonian Pernicious Anæmia.

We may now turn our attention again to our original strand, and endeavour to trace where Addisonian pernicious anæmia takes its place in the pattern we have woven. The first reports of the marked response of the blood dyscrasia of this malady to a few microgrammes of vitamin B_{12} began a new chapter in our understanding of the underlying metabolic disturbance responsible for it, and provided a simple and certain means of treatment.

Vitamin B_{12} is now known to replace completely the injectable liver extracts. When it is administered orally to human beings, small amounts are effective only if they are accompanied by a source of intrinsic factor, which is best provided by normal gastric juice. Patients with typical pernicious anæmia—those with characteristic megaloblastic bone marrow, gastric atrophy and complete achlorhydria—do not respond to vitamin B_{12} *per os* unless relatively huge doses are given. The effectiveness of small amounts by this route is very much less than that of similar quantities administered parenterally. However, if gastric juice accompanies the vitamin B_{12} administered *per os*, the magnitude of response is sometimes of the order of that elicited by injection of an identical quantity. Although the nature of intrinsic factor and the way it functions are becoming better understood, discussion of the properties of the group of substances with which vitamin B_{12} combines to form complexes that pass easily through the wall of the gastro-intestinal tract must be set aside on this occasion.

The early claims that the disordered erythropoiesis of Addisonian pernicious anæmia responded favourably to injection of massive quantities of the deoxyriboside thymidine were of very considerable theoretical interest, and upon them a plausible hypothesis to explain the function of vitamin B_{12} in the genesis of red cells was erected. There is little doubt that vitamin B_{12} enters in some essential way into the course of events of intermediary metabolism, through which the single carbon atom of formate is transferred to the 5-position of the pyrimidine ring and reduced there to the 5-methyl group of thymine. Moreover, the enzyme system capable of effecting this methylation is known to be widely distributed; it has been studied, for instance, in such diverse systems as cultures of bone-marrow cells and of *L. leichmannii*. However, the primary and only essential role played by vitamin B_{12} in *L. leichmannii* is probably its function in the metabolic channel through which the pyrimidine deoxyribosides are elaborated, because this microorganism's normal nutritional requirement for vitamin B_{12} may be met not only by thymidine, but also, it has been claimed, by other pyrimidine deoxyribosides.

The suggestion that vitamin B_{12} functions in the process of erythropoiesis merely by effecting a methylation thus received less collateral support than previously from nutritional studies of *L. leichmannii*. Its mainstay—i.e., the claim that an erythropoietic response could be elicited by injection of thymidine—has been thrown open to doubt by recent observations that thymidine, if carefully purified, is quite inactive in this respect, and by the suggestion that the earlier observations made after injection of crude preparations isolated from liver were probably due to vitamin B_{12} present as an impurity. The similar claim that the blood dyscrasia responds to ingestion of orotic acid (uracil-4-carboxylic acid) is also of theoretical interest, for there is evidence that this derivative of carbamyl-L-aspartic acid is an intermediate in the synthesis of pyrimidines *in vivo*. However, in comparison with those elicited by vitamin B_{12} and by folic acid, the reported responses to massive doses of orotic acid are small and transitory.

The underlying reason for the fact that, in the metabolic chain of events responsible for red-cell production, vitamin B_{12} and folic acid are to a very considerable extent interchangeable, remains a mystery.

It is possible that the disordered erythropoiesis in Addisonian pernicious anæmia stems from an impairment of a single metabolic process, but this is not yet evident. Whatever the impairment, it is subsidiary to a more fundamental metabolic lesion, which is deeper set, more complex and less affected by folic acid.

Possibly a prediction that the basic metabolic defect supervening on a shortage of vitamin B_{12} is likely soon to be satisfactorily understood may not lead to a charge of unwarranted optimism. At least we may rest assured that search for it will yield still more bounty, to further the eminently practical ends of human medicine and of agriculture.

Concluding Remarks.

I propose to leave the cobalt story at this stage. Like all other stories of the progress of scientific understanding, none of its chapters is in any sense complete. Each accession to knowledge of the biological functions in which cobalt plays a part has opened up new vistas, sometimes of great beauty, to fascinate and encourage all whose curiosity leads to an interest in this aspect of nutritional physiology.

Mr. Chairman, it is usual in formal lectures to provide, in summary, a few words that may guide and give confidence to others working in the particular field that has been the subject of discussion. I propose then, on this occasion, to conclude by reading a few words out of a letter received a day or so ago from my good friend and mentor, Dr. Elmer V. McCollum, Emeritus Professor of Biochemistry of Johns Hopkins University, who is—as you all know—one of the few surviving worthies of the small group who built the bases of the newer knowledge of nutrition, and beloved doyen of nutritional physiologists everywhere. Remarking upon the correction of a metabolic disorder in one of his disciples, he wrote:

> The presently known successes in treatment of human disorders by replacement therapy afford clear evidence that when biochemistry of metabolism has been sufficiently explored experimentally, further great achievements in curative medicine are sure to come. Viewed from our present hill-top horizons it seems to me that biochemistry promises more for the future of the human race than any other segment of knowledge. The results of the comprehensive programme of research on nutrition and agriculture form one of the enduring monuments of scientific progress . . .

I think we may continue our search with that thought in our minds; no doubt similar thoughts led Dr. Annie Cunning to the decision to initiate the lectures that bear her name.

Bibliographical Note.

No attempt will be made here to provide a bibliography, as even after abridgement a reasonably comprehensive list of references would entail several hundreds of items.

The earlier literature and a review of the nutritional significance of cobalt, the discovery of vitamin B_{12}, animal protein factor, etc., up to 1952, will be found in "Cobalt, Copper and Molybdenum in the Nutrition of Animals and Plants", by H. R. Marston, *Physiol. Rev.*, 32: 67.

References to more recent advances in the knowledge of chemistry, structure and metabolic function of vitamin B_{12} may be found in "Vitamin B_{12} und Intrinsic Factor", which is the report of the European Symposium devoted to that title held at Hamburg in 1956, edited by H. C. Heinrich and published in 1957 by Ferdinand Enke Verlag, Stuttgart.

Most of the references relevant to the vitamin B_{12} requirements of protists and protozoa will be found in "The Biochemistry and Physiology of Protozoa", two volumes of reviews edited by S. H. Hutner and André Lwoff, and published by Academic Press Inc., New York, in 1955.

Remarks that refer to the roles of cobalt and vitamin B_{12} in the metabolism of ruminants have been based on experimental investigations conducted in the author's laboratory. Reports of a long series of these studies are being prepared for publication in the scientific literature.

DIABETES MELLITUS IN CHILDREN—RECENT ADVANCES.

By S. E. J. ROBERTSON,
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THERE have been no fundamental changes in the causation or management of diabetes mellitus in children of recent years. The sulphanyl compounds appear to have no place in the treatment of diabetics who have little or no source of endogenous insulin, and all child diabetics appear to be of this type.

However, I have been in charge of the Diabetic Clinic at the Royal Alexandra Hospital for Children since 1952,

during which period 89 cases of diabetes have been diagnosed in children under the age of 13 years and these have been observed at regular intervals since. During this period, observation of these patients has led me to formulate certain theories as to management, which have been utilized in practice and which may be worthy of record.

The ætiology continues to be obscure. Inheritance obviously plays a part, but on no occasion has the disease been observed in siblings. On one occasion the disease appeared in the mother some years after it was detected in her child. Some precipitating factor is often found, which may be in the nature of a febrile illness, such as measles or mumps, or of a shock. One child developed thirst and polyuria on the night after a launch accident on the harbour during the day.

Study of the presenting symptoms has been of great interest. Infants under the age of 12 months often have their disease discovered by accident. The youngest, aged five months at diagnosis, presented to her doctor as a well child with a napkin rash. He found a heavy sugar content in her urine on a routine examination. Others are found to have heavy glycosuria when admitted to hospital because of feeding difficulty or loss of weight. However, infants who are unduly thirsty and who are not gaining weight may have diabetes, and it is possible that cases of diabetes in infancy have often been missed in the past because of a failure to test the urine routinely for sugar.

Older infants and young children have the same thirst and polyuria, loss of weight and lassitude as adults, but rarely have excessive appetite. However, the interval between the onset of thirst and polyuria and the onset of serious acidosis is often short, and many children present with well-developed signs of diabetic coma. One child was admitted to hospital in deep coma, whose thirst and polyuria had been noticed by the parents only 24 hours previously.

The polyuria and thirst of children with diabetes are severe, and large quantities of fluid are drunk and passed as urine. Commonly, a nervous, irritable child with a poor appetite is taken to the doctor for a physical check. The doctor finds that the child frequently asks for a drink and just as frequently wants to pass water. However, the quantity drunk is rarely more than a mouthful, and the quantity passed as urine rarely more than an ounce. Should a trace of reducing substance be found in the urine of such children, diabetes is suspected and the child referred to hospital. This mistake often causes a great family upset and makes a nervous child more nervous. I should like to state that the polyuria and thirst of childhood diabetes are severe and that glycosuria is heavy. If these three findings are not present, the child almost certainly has not got diabetes.

Children with diabetes do not get pustular infections more than other children. Similarly, non-specific vulvovaginitis with pruritis vulvæ, so common in young girls, is not associated with diabetes in children unless accidentally.

As a rule the diagnosis can be made quite firmly on the clinical features of thirst, polyuria and heavy glycosuria alone, but if confirmation is necessary, a blood sugar level estimation from blood taken at random is all that is required. If this level is over 250 mg. per 100 ml., the diagnosis is confirmed and treatment with insulin should be started immediately. The standard glucose tolerance test has been abandoned as being unnecessary. It is also contraindicated, as it takes several days to a week to arrange, and owing to the rapidity with which serious acidosis in the untreated diabetic can occur in this age group, this delay may be dangerous.

Owing to the rapidity with which acidosis may develop in the untreated diabetic child, the patient may be sent to hospital unconscious, with a provisional diagnosis of meningitis. However, the deep, rapid breathing of diabetic acidosis is unmistakable. In the last year, two children have been seen in deep coma with air hunger whose blood sugar level was normal. Both these children had severe staphylococcal septicæmia with metabolic acidosis. Another child with a similar clinical picture had renal failure and another aspirin poisoning.

The laboratory figures in diabetic coma have been fairly uniform. The blood sugar level is little guide to the depth of the coma, being anywhere between 400 and 2000 mg. per 100 ml. The serum bicarbonate level is below 12 mEq/l. and usually much lower. The figure for sodium, despite severe deficiency, is usually normal, as are those for potassium and chloride.

The management of diabetic coma has been successful, there having been no fatalities. This success has been largely due to the ability of the children to recover from a serious fluid and electrolyte disturbance because of their uniformly good renal functions and the absence of cardiac weakness if treatment supplies any deficiency. The principles of treatment are to replace fluid and sodium deficiency, to give alkali to reduce the acidosis and to give potassium salts early. Insulin is vitally necessary of course, but is not as important as restoration of the body fluids to normal.

Children have small veins, and as a rule a cut down on the saphenous vein at the ankle and the insertion of a cannula or plastic tube is necessary. Fluid loss is always severe, and 10% of the patient's weight is given in the first four to six hours. This would, for example, entail giving one litre of fluid to a child weighing 10 kg. or 22 lb., aged 12 months, at a rate of 60 drops a minute; or three litres to a child weighing 30 kg. or 66 lb., aged 10 years, at 180 drops per minute, which is as fast as the usual Murphy's drip can go. Recently a child, aged 11 years, required seven litres of fluid in the first 24 hours for adequate rehydration.

It is usual at the Royal Alexandra Hospital for Children to give this rehydrating fluid as a solution of half-isotonic sodium chloride with 2·5% dextrose, with 50 milliequivalents of sodium bicarbonate added to each litre. However, sodium bicarbonate solution may not be available in some hospitals, in which case it is recommended that each litre of rehydrating fluid should consist of 300 ml. of one-sixth molar sodium lactate solution *plus* 700 ml. of half-isotonic sodium chloride and dextrose solution or half-isotonic sodium chloride solution *plus* 12 ml. of four molar sodium lactate solution in each litre. Such solutions will restore the fluid deficit and largely relieve the sodium deficit in four to six hours as evidenced by restoration of moisture to the oral mucous membrane and of subcutaneous tissue turgor and by rise of the serum bicarbonate level to a safe level and cessation of overbreathing. Children with diabetic coma, as mentioned above, have adequate renal function almost invariably, and any overdosage with either fluid or sodium, both unlikely, will be dealt with by the child.

After this initial rehydration fluid has been supplied, in four to six hours the patient is given what is considered to be his maintenance daily requirements of fluid and electrolytes in the next 18 to 20 hours. The fluid usually used is one-quarter or one-fifth isotonic saline and dextrose solution, to each litre of which is added 30 milliequivalents of potassium. Half this potassium is dipotassium hydrogen phosphate and half potassium chloride. The quantity of fluid given depends on the age of the child, if aged 12 months or more. The child is given one litre, to which is added 100 ml. for each year of age over one. If aged under 12 months, it is given 140 ml. of fluid per kilogram of body weight with a maximum of one litre per 24 hours.

Ordinary soluble insulin in divided doses is used in the initial 48 hours of treatment. The initial dose is two units for each kilogram of body weight. Half of this may be given intravenously and half intramuscularly. No further insulin is given for a period of six hours.

Observations of the patient are made at least every three hours. These consist of pulse rate, respiratory rate and depth, blood pressure, the state of consciousness, and the state of hydration from estimation of eyeball tension, oral moisture and subcutaneous tissue turgor. Urine is collected by means of an indwelling catheter in females or a Paul's tube in males, and its volume measured. Every three hours

the catheter or Paul's tube is disconnected from the collecting bottle and a specimen obtained, which is examined for reducing substances and ketone bodies. Luckily it is almost unknown for children with diabetic coma to have anuria, a factor which perhaps explains the success of treatment.

Laboratory examinations depend on the facilities available. In this hospital the levels of blood sugar and serum bicarbonate with a roughly quantitative estimation of serum acetone are carried out every six hours until the patient's hyperglycæmia and bicarbonate deficit are under control. Estimations of levels of serum sodium, chloride and potassium, while not essential, are usually also done when bicarbonate levels are determined.

Further doses of insulin after the initial dose can be extremely difficult to estimate. The blood sugar level comes under control very quickly, and it is easy to swing the patient from hyperglycæmia to hypoglycæmia. If at the end of the first six hours the blood sugar level has not fallen, the initial dose should be repeated. If it has fallen by between 25% and 50%, half the initial dose should be given. If it has fallen by more than 50% but is still above normal, one-quarter of the initial dose should be given. If the blood sugar level is within normal limits, no insulin should be given at that time. The same rules are followed in estimating insulin dosage after 12, 18 and 24 hours of treatment. It should be remembered that hyperglycæmia does not need rapid correction and that there is a great danger that too much insulin will be given in the first 24 hours.

If blood sugar levels are not obtainable, one must rely on examination of the urine for reducing substances at six-hourly intervals. If the test with Benedict's solution produces a red result at the end of the first six hours, half the initial dose is given. If there is any less reduction in this test, it is safer to give one-quarter of the initial dose or none at all until specimens collected subsequently are examined. Specimens collected after 12, 18 and 24 hours are assessed in an empirical fashion. If the test shows a red result, ten units are given, if orange, eight units, if yellow, six units, and if green or blue, no insulin at all.

It is emphasized that great care should be exercised in insulin dosage after the first 12 hours of treatment, as hypoglycæmia of a severe degree can easily be produced. Should such symptoms occur, a 25% dextrose solution should be injected slowly into the tubing of the intravenous set until symptoms are controlled.

After 12 hours of treatment the patient has recovered a normal degree of hydration and a full degree of consciousness. Often these have been achieved in six hours, but I have often observed deterioration in the degree of consciousness in the second six hours after an initial recovery after six hours of treatment. The reason for this deterioration has not been apparent.

Ketonuria takes longer than glycosuria to disappear, and quite large amounts of ketone bodies may be found in the urine after all other abnormalities have been controlled. This continued ketonuria need cause no concern and is not an indication for increase in insulin dosage.

After 24 hours the patient can take fluids by mouth, and a fluid diet of volume the same as the maintenance requirements defined above is prescribed. This fluid should contain 1000 Calories *plus* 50 Calories per year of age largely as dextrose in orange juice, with broth, weak tea or other suitable fluids. If such fluid is taken and retained, intravenous fluids can be discontinued. If not, maintenance requirements of fluid and electrolytes as defined above should be continued for a further 12 to 24 hours by the intravenous route.

When the patient is taking fluids by mouth and the intravenous cannula has been removed, potassium, in the form of potassium chloride, should be given by mouth in a dose of one gramme three times a day.

After 48 hours of treatment a normal diabetic diet can be prescribed of 1000 Calories *plus* 50 Calories for each year of age. Of these calories half are supplied as carbohydrate. Protein is given as two grammes per pound up to the age of four years and one gramme per pound over that age. The remainder of the calories are made up with fat.

A long-acting insulin can be commenced between 36 and 48 hours after the beginning of treatment. The first dose is given before breakfast, and the dose equals the total amount of insulin given in the previous 24 hours. The management of the patient from then on is the same as for the child diabetic admitted to hospital on diagnosis, but who has no severe acidosis.

The management of diabetic pre-coma is the same in principle as that of coma. Dehydration is not so severe, and usually 5% of the body weight is given as rehydrating fluid. A quarter or one-fifth isotonic saline solution with dextrose is used instead of half isotonic saline solution as this rehydration fluid, but the added bicarbonate is the same, namely, 50 mEq to each litre of fluid. Similarly, 300 ml. of one-sixth molar sodium lactate solution with 700 ml. of one-fifth isotonic solution or 12 ml. of four molar sodium lactate solution to a litre of one-fifth isotonic saline solution can be used. After rehydration requirements are given as described before, to which potassium has been added, insulin dosage initially is the same as are the subsequent doses.

After recovery from the acidosis with disappearance of ketonuria, the appetite improves and the diet has to be increased rapidly.

When a child is admitted to hospital without acidosis or when acidosis has been relieved, management is the same. The child is given a diet which is increased or decreased according to its appetite and allowed up and about the ward. A long-acting insulin is prescribed (in this hospital insulin zinc suspension) in a dose of one unit per kilogram of body weight.

Urine is tested only twice daily, but the specimens tested are always second specimens. That is, the first specimen passed after waking in the morning is discarded and the child passes another specimen before breakfast, if necessary with the aid of a glass of water. This second specimen is tested with Benedict's solution and the result recorded on a chart in coloured pencil. A similar procedure of obtaining, testing and recording a second specimen is carried out before the evening meal.

The dosage of insulin zinc suspension is varied according to the results of these two tests. If an evening specimen contains heavy sugar sufficient to give a red or orange reaction to Benedict's test and a similar result occurs the following morning, the dose of insulin zinc suspension is increased by four units. If both these specimens are blue, the dose is decreased by two units.

A very important part of the treatment and eventual control is started as soon as possible, namely the training of the mother. She attends daily to learn simple dietary practices, urine testing, insulin measurement and injection and how to alter the diet and insulin dosage according to the twice-daily testing of second specimens. If the child is over the age of 10 years he can almost always be taught to give his own injections. As a rule the insulin dosage is fairly stable, and the mother is trained to look after the patient about a week after his admission to hospital and is ready for his discharge.

It is of the greatest importance for the insulin dosage to be reduced by 25% on the day of discharge. There is a tremendous difference in the amount of activity of a child in a hospital ward, even up and about, and of a child at home, so that insulin requirement is reduced from this cause. Another very important factor is the drop in insulin requirement which occurs in the newly-diagnosed diabetic child within one or two weeks of control being achieved. Thus a child may leave hospital about ten days after diagnosis on a dose of 24 units and within a few weeks have a dose as low as four units for good control. Non-realization of these two factors can result in a severe hypoglycæmic attack, which may need readmission to hospital, but more important, may totally destroy the confidence of the parents in their ability to manage the disease.

The mother and child should be seen weekly after discharge from hospital for about a month. During this period she varies the insulin according to the rules given below. From observation of the patients at the Royal Alexandra Hospital for Children, it cannot be too strongly emphasized that successful control can be gained only by day to day alteration of insulin dosage according to the varying needs of the child. This cannot be done by the doctor, so it is the parent who must be trained to make these alterations without reference to him. Mothers vary in their ability to do this. An intelligent, capable woman sees that the twice-daily testing of second specimens is carried out regularly and alters the dose according to the results of these tests. A woman who is conscientious but lacks confidence in herself tends not to increase the dose when the results of the urine tests indicate such an increase. She needs encouragement, but eventually manages very well.

The mothers of diabetic children are instructed to vary the dose of insulin to fairly simple rules. Insulin zinc suspension is used in all cases at present. Two second specimens per day are tested with Benedict's solution—one before breakfast and one before the evening meal. If the evening specimen shows a heavy sugar content and the following morning test gives the same result, the dose of insulin is increased by two units. If the evening specimen is free of sugar and the same result is obtained the following morning, the dose is reduced by two units. If a trace or moderate amount of sugar is found in these specimens, or one contains sugar and one not, the dose remains unaltered. Very few mothers cannot follow these simple rules, and it is believed that this control of the dosage from day to day is the main essential in the successful control of a diabetic child.

Records in coloured pencil are kept and produced at each visit to the clinic every four to six weeks. Study of these records has been of great interest. Insulin dosage tends to increase as the years go by, reaching a maximum about the age of 11 years, when more than one hundred units daily may be required, especially for girls. Insulin dosage tends to be lower during week-ends and school holidays, when the child's physical activity is greater. Minor infections cause an increase in glycosuria, but rarely ketonuria in the well-controlled child. Often a child on insulin zinc suspension will show excellent results to the tests in the morning, but a heavy sugar content every evening, or vice versa. This may be only temporary, but if it persists the shorter acting amorphous variety is mixed in, starting with two units and increased by two units at a time until the evening glycosuria has become satisfactory. Should such heavy glycosuria be present only in the mornings, the longer acting crystalline variety is added in the same way.

Perfection of urine tests is not aimed at. The child whose results to urine tests are mostly blue is on the verge of hypoglycæmia, and will become so if a meal is a little late or there is a little extra exercise. The aim is to produce mostly green results to tests with Benedict's solution, with occasional blue or yellow results.

The questions of diet is a thorny one. A weighed diet has been used in this series, half of the calories of which are supplied by carbohydrates. Protein is given in an amount equal to two grammes per pound of body weight under the age of four years and one gramme per pound over this age. The remainder of the calories are made up by fat. There is a greater quantity of carbohydrate in this diet than the 40% usually recommended, but the lower carbohydrate diet is expensive and requires a lot of fat to make up the necessary calories. The number of calories given in the diet depends entirely on the child's appetite. A hungry child will take food himself, so as soon as the diet in use no longer satisfies him, his diet is increased by 100 Calories, maintaining the same proportion of carbohydrate, protein and fat as in his original diet.

I have no knowledge as to how many diabetics keep strictly to their prescribed diet. Accurate information on this is naturally difficult to obtain. Minor variations from diet are not frowned upon, the principle aimed at being to avoid excessive alterations above or below a standard calorific intake each day.

The "free" diet has not been used at this clinic, but has been used in my private practice, where a proportion of children are attending boarding schools. Special diets are difficult or impossible to obtain at such institutions, and where a child can only obtain an education satisfactory to the parents in this way, he has been allowed the usual diet of his school, supplemented by extra protein. Such children require larger doses of insulin and heavy glycosuria is more frequent, but whether later degenerative complications are more likely remains to be seen.

I believe, myself, that diabetes is treated by insulin and that diet is a secondary consideration. There is a tendency to keep the dose too low in the mistaken belief that a higher dose means the disease is getting worse. It is of the greatest importance for the child's urine to be tested regularly and his dose to be changed frequently, but too strict a watch on diet only leads to resistance in the child and evasion by the parent. Normoglycæmia throughout the whole 24 hours in a rapidly growing individual is almost impossible to obtain, as we have found by carrying out blood sugar tests at six-hourly intervals on children in hospital. On a strictly weighed diet with adequate doses of insulin and with the child in bed there will be wide swings in the blood sugar levels at different times on different days, for which no reason can be found. The too strictly controlled child is frequently on the edge of hypoglycæmia, and the constant discipline which such an aim entails frequently leads to emotional disturbances. I think it was Lawrence who said that the purist physician may gain great intellectual pleasure from strict control of his patient's blood sugar level, but is a curse to the patient.

The prevention of hypoglycæmia in children is of the greatest importance. Severe hypoglycæmia, especially if prolonged or repeated, is likely to be associated with permanent brain damage. Epilepsy and electroencephalographic changes have been found in four cases, in three of which hypoglycæmia can be blamed. Two children had severe hypoglycæmia after overdosage of a long-acting insulin; the fall in insulin requirement, which was not anticipated, occurred soon after the initial stabilization. Both exhibited a strange but identical clinical picture of severe epilepsy of the mixed *grand mal* and *petit mal* variety, were very difficult to control, and had mental retardation and a bizarre type of precocious puberty.

Minor degrees of hypoglycæmia must be expected in any well-controlled child, but should never be allowed to get beyond the stage of pallor, sweating and excitement or nervousness, when the prompt administration of half a teaspoonful of sugar from the household sugar pot will relieve it. Late meals should be prohibited and unusual exercise balanced by some plain biscuits and cheese immediately before or after. In a normal day, the danger period is between waking and breakfast and the hour before the midday or evening meals, and if these periods produce mild symptoms of hypoglycæmia, the dosage should be reduced.

Hypoglycæmia severe enough to produce loss of consciousness necessitates the patient's admission to hospital immediately, where sugar can be given intravenously or by tube, and the blood sugar estimations carried out. When consciousness is not recovered despite raising of the blood sugar level to above normal, a difficult problem arises, as the hypoglycæmia must have caused irreversible changes in the neurones by raising the blood sugar level. Such a patient has not been encountered at the Royal Alexandra Hospital for Children since the discovery of the corticosteroids, but I feel that one of these preparations should be used in such cases in large doses.

Pre-operative and post-operative management of diabetic children is difficult. Emergency operations need management similar to that of diabetic coma, with intravenous fluids in maintenance amounts and if possible laboratory estimations of electrolytes and blood sugar. With elective operations the problem is more difficult. I should advise against the giving of strong glucose solutions by mouth within several hours of operation. They may be retained

in the stomach and vomited and inhaled during the anæsthetic with the most terrifying results, as happened to one of our patients. All elective operations on diabetic children should be carried out in a hospital which can estimate blood sugar levels throughout the 24 hours. It is then possible to give the child a small carbohydrate breakfast on the morning of operation with one-third of his usual insulin dose given as soluble insulin. At mid-morning his blood sugar content can be estimated, and if it is normal or high, operation can be carried out about mid-day. The surgeon must of course be punctual. If it is low, an intravenous infusion should be started and the child given glucose by vein in a 5% solution until several hours after the end of the operation. An anæsthetic should be used which is not associated with post-operative vomiting. After operation close watch is kept on the blood or urine sugar level. Small feeds of carbohydrate are given by mouth and small doses of soluble insulin given accordingly, equal in size to one-third of the daily insulin requirement.

Finally, I should like to mention a very important aspect, which is the training of the child to manage his own disease. We do not see diabetic children after their thirteenth birthday, but it is common knowledge that they are extremely difficult to manage both in control of their diabetes and in their emotional problems. I wonder if at least part of these difficulties is not due to their being too close to their parents in childhood. The parent watches their diet, tests their urine and administers their insulin, and the child without his parent is lost. It is felt strongly that as early as possible, and certainly by the tenth birthday, diabetic children should give their own injections, test their own urine, keep their own records and at least know what foods should be avoided. When these have been attained, they can stay with friends, go camping, and apart from the necessity of having injections and watching their diet, be the same as other children.

Acknowledgements.

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THE LABORATORY DIAGNOSIS OF VIRUS DISEASES.[1]

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THE term "virus" has been defined in various ways. Syverton (1957) defined a virus as a "nucleoprotein particle capable of inducing its own replication by susceptible cells, on which it is dependent, and yet to which it is essentially foreign". The viruses differ from bacteria in several ways, first in being smaller and (in most cases) invisible to the light microscope; more importantly, they differ in being unable to grow except in living cells. Virus genetic material assumes control of the metabolic processes of the infected cell and diverts them to the production of more virus. They are therefore, in most cases, not susceptible to chemotherapy, as inihibition of virus growth would need to involve inhibition of host cells. Once they have entered the host cell they are also protected from the action of circulating antiserum. While antibiotics have made the bacterial diseases amenable to treatment, the relative importance of virus diseases has increased.

[1] Part of a symposium on virus diseases read at a meeting of the Queensland Branch of the British Medical Association on June 6, 1958.

The term "virus" covers a wide range of organisms, with in some cases little basic similarity. No really satisfactory classification has yet been put forward, but the viruses tend to form themselves into certain obvious groups, which may serve as a basis for discussion. Thus we recognize the psittacosis-lymphogranuloma group, which in their size and antibiotic sensitivity have more in common with rickettsiæ than with other viruses, the enteric virus group, including the poliomyelitis viruses and their cousins, the arthropod-borne encephalitis group, and the viruses of the exanthemata, to name only a few. These are well-defined viruses, capable of study in experimental systems. There are a diminishing number of diseases presumed to be due to a virus, but in which no agent has ever been transmitted to any experimental animal except the human volunteer, e.g., rubella, and infectious and serum hepatitis. Finally, there are diseases which have not been satisfactorily transmitted even to human volunteers (e.g., infectious mononucleosis), but which are nevertheless considered to have a virus ætiology. Only the viruses capable of study in the laboratory are as yet the concern of a virus diagnostic laboratory. It is proposed tonight to deal mainly with two groups of virus diseases — those of the central nervous system and those of the respiratory tract. Before we focus down on these groups, I should like to discuss, very briefly, some of the techniques involved in virus studies, first because progress in virology has followed closely on the development of new techniques, and secondly because some knowledge of the limitations of these techniques will be necessary for the practitioner to use a virus diagnostic laboratory satisfactorily.

The earliest method of virus isolation was by inoculation of infectious material into human volunteers. This method must still be used in certain instances. For example, what knowledge we have of infectious hepatitis virus was gained in this way. In most cases, fortunately, it has been possible to find suitable experimental animals. Thus, in 1908, Landsteiner transmitted poliomyelitis to a monkey by inoculating human cord into its brain. In this case the disease in the monkey resembled that in a man, but this is not always so. Thus yellow fever produces a systemic illness with jaundice in man and the monkey, but encephalitis in the mouse. The latter animal, being cheap and readily available, became the standard tool for studying yellow fever virus and a number of other viruses. A major advance was the introduction of the embryonated egg in the 1930's. Many viruses were found to grow when inoculated by one route or another. Thus the virus of smallpox produces pocks on the chorio-allantoic membrane; influenza virus grows in the amniotic or allantoic cavities; psittacosis virus will grow in the yolk sac. The use of new-born mice led, in 1947, to the isolation of a whole new group of viruses — the Coxsackie viruses. The study of cells in tissue culture, commenced by such people as Alexis Carrel early this century, was soon applied to virus culture. At first the methods were cumbersome, but even so they were responsible for such successes as the attenuation of yellow fever virus and the production of a vaccine. In 1947 it was shown that poliomyelitis virus would grow in cultures of non-nervous human or monkey tissue. This led to the intensive use of tissue culture; the techniques were simplified and applied to many viruses, with an alarming production of "new" viruses. The modern virus laboratory must use each of these tools, especially mice, eggs and human-cell tissue cultures.

Techniques of virus isolation are only half the story. Equally important are the means for detecting antibodies to the virus in patients' convalescent serum. In some cases these methods are the same as those used in diagnostic bacteriology. Thus the complement fixation test is widely used, and agglutination of psittacosis elementary bodies by antiserum can be demonstrated. The basic serologic technique in virology is the neutralization test. In its simplest form this involves the mixing of a known quantity of virus with the serum to be tested and the inoculation of the mixture into susceptible

animals. If antibody is present, the virus is neutralized and the animals survive. In 1941 it was found that influenza virus was able to clump chicken red blood cells. This phenomenon has been demonstrated with a number of viruses; the agglutination can be inhibited by immune serum, allowing in many cases a simple and quick diagnostic test. In other cases, in which red cells are not agglutinated, it may be possible to coat them with virus material, so that antiserum to the virus will agglutinate the coated cells. The union of virus and antibody may be seen in some instances by antibody being tagged with fluorescein, and examined by ultra-violet light microscopy. One or other of these techniques can be employed to demonstrate the appearance of antibodies. The choice of technique will depend on the virus, on the cost (in-vitro tests usually being cheaper than neutralization tests) and on the information desired. Thus both complement fixing and neutralizing antibodies develop after infection with Murray Valley encephalitis; the latter remain in high titre for many years, the former usually fall below a detectable level within about two years.

These considerations may be applied to one of the two groups of viruses under discussion tonight. The following are some of the viruses that may be concerned with acute infections of the central nervous system, presenting clinically as encephalitis, meningo-encephalitis or aseptic meningitis: poliomyelitis types 1, 2, 3; lymphocytic choriomeningitis; mumps, herpes simplex, arthropod-borne encephalitides, Coxsackie group B and type A9; E.C.H.O. types 4, 6, 9; encephalomyocarditis; lymphogranuloma venereum. This is not a complete list; it omits a number of diseases of proven or suspected virus ætiology in which such complications have been described (e.g., infectious mononucleosis), and omits also the demyelinating encephalitides that may follow the exanthemata and certain inoculations. Let us consider what measures would be taken to investigate a patient with an acute virus infection of the central nervous system.

Virus isolation would be attempted from brain or spinal cord (in fatal cases), cerebro-spinal fluid, fæces or blood. These would be inoculated into the brains of new-born mice, into human cell cultures and into eggs. Death of mice, degeneration of cells or lesions in eggs might indicate the isolation of some agent, but it would be necessary to confirm that such changes were due to a virus and not to bacteria or toxic material, such as might be present in fæces. The pattern of degeneration, the histopathology of infected animals and the material from which virus was isolated may give some indication of what the virus is. Thus the virus of poliomyelitis may be isolated from fæces or spinal cord in tissue culture, but not in mice or eggs. The Coxsackie viruses may be isolated from fæces or occasionally from cerebro-spinal fluid; they may produce degeneration in culture cells, but will produce typical lesions in mice. The E.C.H.O. viruses can be isolated from fæces or cerebro-spinal fluid in tissue culture only. The virus isolated must be identified by serological means; this is usually done by showing that it is neutralized in a suitable host by a known antiserum.

It is necessary also to demonstrate that the patient's serum develops antibodies to the virus isolated. If no virus is isolated, it may be still possible to prove the diagnosis by testing the serum against viruses considered possible causes of the disease. The labour and amounts of serum that would be needed prohibit most laboratories from offering to test for all the viruses listed on a routine basis. However, a judicious selection can usually be made. Thus patients with encephalitis in summer in Australia should be tested for antibodies to Murray Valley encephalitis. Patients with aseptic meningitis in the absence of an epidemic of poliomyelitis, Coxsackie or E.C.H.O. virus infection might reasonably be tested for poliomyelitis, herpes simplex, lymphocytic choriomeningitis and mumps.

The laboratory results, when completed, must be carefully assessed. The enteric viruses (poliomyelitis, Coxsackie and E.C.H.O.) occur on occasion in normal people, and may produce sub-clinical infections; their isolation and the demonstration of a rising titre of antibodies may be coincidental and have nothing to do with the illness under investigation. Rising titres may be due to cross reaction (thus Murray Valley encephalitis complement-fixing antibodies may be due to dengue) or to anamnestic response. The first serum must be taken very early in the disease, or it will not be possible to determine whether antibodies detected were due to the current illness or to one that occurred perhaps many years before. On the other hand, antibodies may not appear until four to six weeks after infection; hence repeated convalescent samples may be necessary. Death from encephalitis may occur before antibodies could appear, leaving virus isolation as the only possible means of diagnosis. Diseases not caused by viruses must be excluded; thus leptospirosis is not an infrequent cause of meningitis, and most virus laboratories have referred to them, patients who eventually prove to have such diseases as cerebral abcess, cerebral tumour, torulosis or tuberculous meningitis. Finally, there are central nervous system virus diseases in which laboratory diagnosis is not possible or is not practicable (e.g., herpes zoster meningitis). The final diagnosis must rest with a careful assessment of the combined clinical, pathological and laboratory findings.

The percentage of infections of the central nervous system finally diagnosed varies with the time and place. In the presence of a recognized epidemic, such as that due to Murray Valley encephalitis virus in N.S.W. and Victoria in 1951 or that due to E.C.H.O. type 9 in Europe in 1954-1955, a high percentage of diagnoses were confirmed in the laboratory. The score is lower with the sporadic cases usually studied in large city hospitals. Thus, of 120 cases of aseptic meningitis in Philadelphia, 78 remained undignosed, 10 were diagnosed as Coxsackie group B virus infections, 13 as mumps, 8 as lymphocytic choriomeningitis, 2 as herpes simplex virus infections and 9 as poliomyelitis (Hummeler, 1957).

Virus diagnosis has made rapid advances, and diagnostic facilities will undoubtedly become more widely available than they are now. Careful study of clinical material by the techniques available can produce epidemiological data on the spread of virus disease, and may eventually allow us to distinguish individual entities among the mass of cases presenting as aseptic meningitis or as upper respiratory infection. It would be well, however, to emphasize that virus diagnosis has, as yet, much less to offer the individual patient. Results will rarely be available until long after the patient has recovered or died. Virus diagnostic tests are expensive in time, money and effort, and laboratories will have to restrict their tests to cases in which specimens can be obtained at the optimal periods. The onus of diagnosis at present, and for some years in the future, must lie with the physician who attends the patient.

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VIRUS INFECTIONS OF THE NERVOUS SYSTEM.[1]

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VIRUS INFECTIONS of the nervous system play quite a large part in the practice of a physician interested in infectious diseases. In this paper I wish to discuss the broader aspects of virus infections rather than present a detailed study of individual diseases. Several general points of importance need to be discussed first.

[1] Part of a symposium on virus diseases read at a meeting of the Queensland Branch of the British Medical Association on June 6, 1958.

1. Is the condition under consideration in fact caused by a virus? This question may be extremely hard to answer. Many diseases are commonly ascribed to virus infection when proof is lacking. In other diseases the causal virus may be readily isolated if facilities are available. In most cases clinical diagnosis is all that is possible. At times clinical diagnosis can be certain; at others it is merely a shrewd guess.

2. If the condition is in fact due to a virus, what part of the nervous system is involved? The terms meningitis and encephalitis are often used rather loosely. As far as possible the clinical diagnosis should indicate whether meningitis or encephalitis is present. Frequently both meninges and brain are involved, and sometimes there is extension to the spinal cord as well. However, clinically it is often quite impossible to define the dividing line between these conditions, even though they may be quite distinct at post-mortem examination.

3. Different agents may produce identical pathological features in the brain. This is particularly important in the group of demyelinating encephalitides occurring during the course of some of the common infectious diseases such as measles and chicken-pox. The similarity of the encephalitis following these very different infectious diseases has led to the supposition that the brain damage is the result of an allergic process, but such a hypothesis has not yet been proved. An alternative supposition is that the initial infection activates a virus, previously latent, and that it is this virus rather than that of the original infection which produces the encephalitis. However, no such demyelinating virus has yet been isolated, and all known neurotropic viruses produce quite different changes.

The following is a tentative classification of virus diseases of the nervous system. This list is not complete. I have deliberately left out many diseases which have been reported once or twice only, and I have also left out many "laboratory" illnesses in which the disease has been contracted accidentally by workers in the laboratory, but in which the infection is not a natural disease of man. Some of these infections listed do not occur in Australia, but they are included because of their medical significance.

1. Peripheral nervous system: Herpes zoster, ? peripheral neuritis, ? Bell's palsy.
2. Central nervous system:
   - A. Aseptic meningitis: (i) Transmitted by man—infectious mononucleosis, mumps, Coxsackie virus infection, lymphogranuloma venereum; (ii) transmitted by rodents (mice)—benign lymphocytic choriomeningitis.
   - B. Encephalitis or myelitis (due to a neurotropic virus): (i) Transmitted by man—poliomyelitis or polioencephalitis, mumps, herpes simplex, herpes zoster, epidemic encephalitis type A (encephalitis lethargica); (ii) transmitted by arthropods—epidemic encephalitis type B (Japanese and St. Louis), Murray Valley encephalitis, equine encephalitis; (iii) transmitted by animals—rabies; (iv) others, known and unknown.
   - C. Demyelinating encephalitis (following virus infections and vaccination): Measles, rubella, chickenpox, smallpox, smallpox vaccination, mumps, influenza.

Before dealing very briefly with individual diseases, I should like to make a few general points regarding symptoms, pathology and treatment. The symptoms, in general, are those of meningeal or brain inflammation, often associated with raised intracranial pressure. In some cases specific features of diagnostic significance may occur, such as the rash of herpes zoster or the lower motor neurone paralysis of poliomyelitis, but in others there may be none, and one has to be content with a non-specific diagnosis such as aseptic meningitis. Toxic delirium, meningismus associated with an infection such as tonsillitis or pneumonia, or anoxia due to respiratory inadequacy or obstruction must of course be considered and excluded, if possible, before a diagnosis of meningitis or encephalitis is made.

As mentioned previously, these conditions are not all separable pathologically. The major pathological findings are lymphocytic infiltration of the meninges, nerve cell degeneration, perivascular cuffing with plasma and mononuclear cells and demyelination. Gliosis occurs later. Many or all of these features may exist together in the one condition. The cerebro-spinal fluid may be normal or abnormal. Frequently, in the most devastating illnesses, it is normal in all respects; in others there may be many hundreds of cells in the fluid with no clinical evidence of meningitis. Examination of the cerebro-spinal fluid therefore may not be of much value in these conditions, except to exclude bacterial or fungal meningitis.

Treatment is as yet of little avail. Specific treatment is available for a very few, such as the lymphogranuloma group (some authorities would remove these organisms from the class of virus and classify them as rickettsial). Specific prevention is available for others, such as poliomyelitis and rabies. But in general the treatment of the disease is symptomatic only. The injection of convalescent serum has been strongly recommended in the past, but without convincing results. Recently, cortisone has been tried in the group of demyelinating encephalitides, but as a rule the results are not dramatic and it has yet to find its rightful place.

Peripheral Nervous System.

Herpes Zoster.

Herpes zoster is a relatively common disease. The virus is present in the affected posterior root ganglion and in the skin vesicles, and it appears to be identical with that causing chicken-pox. It is said that some degree of meningitis is almost invariably present with herpes zoster infection, even though clinical signs are absent. Occasionally aseptic meningitis and encephalitis are clinically evident, and the death has occurred of some patients with the latter.

Peripheral Neuritis.

It is possible that some types of polyneuritis are due to virus infection, but proof is still lacking.

Bell's Palsy.

The acute onset of facial paralysis in young people, frequently after a mild cold or fever, suggests that one cause at least of this condition may be viral neuritis. However, as with peripheral neuritis, there is as yet no proof.

Aseptic Meningitis.

Russell Brain's definition of this condition is "an acute infection of the meninges occurring in the absence of any evident focal cause of infection, characterized by the rapid onset of symptoms of meningeal irritation, a pleocytosis in the cerebrospinal fluid and the absence of bacteria from films and cultures of the fluid, and running a benign course".

Viruses frequently cause aseptic meningitis, but they are not the only cause. Leptospirosis, for example, is an occasional one occurring locally. Viruses other than those listed have at times been labelled as causative agents, but it is difficult to mention them all and I have concentrated on the more generally recognized ones.

Infectious Mononucleosis.

Infectious mononucleosis is a common disease, although neurological complications are rare. Aseptic meningitis, encephalitis and polyneuritis have been described, and while recovery generally occurs, deaths have been reported. In the absence of other manifestations of the disease, such as fever, rash, enlarged glands or exudative tonsillitis, the diagnosis may be obscure until the Paul Bunnell test returns a positive result. It is important to note that even though this disease is commonly regarded as being caused by a virus, no such causal virus has yet been isolated, and attempts to transmit the disease to other animals or to human volunteers have apparently been unsuccessful.

Mumps.

The incidence of neurological complications in mumps is uncertain, but it is probably quite high. Amongst patients in hospital, estimates of 25% or more have been

made, but in general it is only the patients with the more severe symptoms who are admitted to hospital, and the over-all incidence is almost certainly not as high as this. Meningitis is by far the commonest manifestation. The patients are moderately ill for some days with high fever, headache and vomiting, but recovery is the rule and residual symptoms are exceptional. Isolated nerve lesions, such as facial paralysis or deafness, occur rarely; hemiplegia and polyneuritis have been reported. It is probable that these result from destruction of nervous tissue, either by the virus itself or as part of a demyelinating process, rather than from the aseptic meningitis.

Coxsackie and E.C.H.O. Virus Infections.

With improving technique, viruses of the Coxsackie and E.C.H.O. groups are being isolated from patients suffering from a variety of conditions. It does not necessarily follow that the viruses are therefore causal, but most authorities now accept that they do cause one type of aseptic meningitis. These cases are generally indistinguishable clinically from non-paralytic poliomyelitis. At times the aseptic meningitis may be associated with the pain of epidemic pleurodynia (Bornholm disease), and then clinical recognition may be possible. Cases of paralysis have been recorded in which Coxsackie but no poliomyelitis viruses have been isolated, but it is not yet generally agreed that paralysis may be caused by Coxsackie virus infection.

Lymphogranuloma Venereum.

Lymphogranuloma venereum is an uncommon disease in this part of the world. Even where it is common, neurological complications are rare.

Benign Lymphocytic Choriomeningitis.

Benign lymphocytic choriomeningitis is caused by a virus normally present in mice and transmitted to man accidentally by contact with mice excreta. No proven cases have yet been reported in Australia.

Encephalitis or Myelitis Due to a Neurotropic Virus.

Poliomyelitis.

Poliomyelitis is the commonest disease in this group, and its clinical description would be out of place in this article. However, it is well to remember that only a small proportion of people infected with poliomyelitis virus develop symptoms, and only a proportion of those who develop symptoms become paralysed.

Polioencephalitis.

Polioencephalitis is relatively rare. It is now recognized that many symptoms of so-called polioencephalitis, such as restlessness and delirium, are in fact due to anoxia associated with respiratory insufficiency, and when the latter is corrected the symptoms disappear.

Herpes Simplex.

Herpes simplex again is a common disease. Neurological complications are very rare, but occasionally they do occur. The clinical picture is that of acute meningoencephalitis. There is widespread destruction of the cerebral cortex and an associated severe leptomeningitis. The mortality rate is high; most patients die within one to two weeks of onset.

Epidemic Encephalitis.

Epidemic encephalitis type A or encephalitis lethargica sprang into prominence as a result of the epidemics just before and after 1920. Of later years it has not assumed epidemic form and it is now rare to see it in acute form. Because of its widespread and epidemic nature, it has been presumed to be due to a virus, but no such virus has yet been isolated. Because it is a chronic and frequently progressive disease, it is also assumed that the virus remains active in the patient's brain for the rest of his life. The clinical descriptions of the acute and chronic stages are well known and need no further elaboration.

Epidemics of epidemic encephalitis type B have been reported abroad, but so far do not appear to have occurred in Australia.

Murray Valley Encephalitis.

Murray Valley encephalitis has been the most important epidemic encephalitis of recent years in Australia. The disease is now known to be identical with the Australian "X" disease of the years after the Great War. The virus has been isolated, and serological tests are available for diagnosis, although retrospectively as far as the individual patient is concerned. It is a very severe disease, carrying a mortality rate of 30% or more and the possibility of permanent sequelæ if recovery occurs.

Equine Encephalitis.

Equine encephalitis is a disease of horses occasionally transmitted to man, and is, I think, unrecognized in Australia.

Rabies.

Rabies is mentioned only in passing. In Australia it is unknown, but in some parts of the world it is still an important part of medical practice.

Other Viruses.

Other viruses are known to cause encephalitis occasionally. As yet unknown viruses almost certainly cause encephalitis as well. Reports appear from time to time of outbreaks of encephalitis occurring in certain communities, such as that in the Royal Free Hospital in London in 1955-1956. It is generally presumed that a virus is responsible for such outbreaks, even though it cannot be isolated.

Demyelinating Encephalitis.

Demyelinating encephalitis follows many of the specific infectious fevers. The pathological features are very much the same in any of these conditions, but clinically there are important differences.

Measles Encephalitis.

Measles encephalitis is fortunately very rare, for when it does occur it is a serious condition. It usually appears four to six days after the onset of the illness when the rash and fever are starting to subside. About 10% of patients die and about 65% of survivors are said to show permanent damage such as hemiplegia, mental defect or epilepsy.

Rubella Encephalitis.

Rubella encephalitis is probably rarer still. It appears in general to be a much milder illness and recovery occurs in most cases, although some deaths have been reported.

Chicken-Pox Encephalitis.

Chicken-pox encephalitis also carries a good prognosis and recovery is the rule. It occurs generally one to two weeks after the appearance of the rash. Incoordination, ataxia and choreiform movements are relatively frequent.

Smallpox.

Smallpox does not occur in this country and encephalitis accompanying it is mentioned only in passing.

Post-Vaccinal Encephalitis.

Post-vaccinal encephalitis is a fortunately rare complication following vaccination against smallpox. Its incidence is variable. In Europe and England soon after 1920 the rate in some areas was apparently as high as one in 5000 vaccinations. In recent times it has been very much less than this. Symptoms occur usually 10 to 12 days after vaccination and are those of severe meningoencephalitis. The mortality rate is about 50%.

Influenza.

Recently, both locally and overseas, cases of demyelinating encephalitis have followed epidemic influenza, and some of these patients have died. However, in view of the vast numbers of patients affected by influenza, it is obviously a very rare complication.

These, then, are the common viral infections of the nervous system. It must be very obvious that there is still much to be learnt about these diseases. Now that virus laboratories are becoming commoner, there is hope that their facilities will be available for the investigation of apparent virus infections, particularly when they appear to be occurring in more than sporadic numbers. Soon the physician may no longer be forced to accept the diagnosis of "encephalitis" without recourse to laboratory help, and this help, when it is available, can only result in raising the standard of our diagnosis and practice.

VIRUS DISEASES OF THE RESPIRATORY TRACT.[1]

By FELIX ARDEN,
Brisbane Children's Hospital.

THE previous speakers have succeeded in conveying to us something of the sense of excitement that attaches to virus studies today. We are passing through a period comparable to the final quarter of the nineteenth century, when the new synthetic dyes, the improved microscope and different culture media were continually revealing new bacteria. Some were pathogenic and some harmless, and physicians had the task of indentifying and classifying the causal organisms of diseases suspected to be of bacterial origin.

With virus diseases of the respiratory tract we face two added complications. On the one hand, the response of mucous membranes to infection does not admit much variety, so that the same symptoms, for example, sore throat, may be caused by more than one virus. On the other hand, a single virus may, under different circumstances, produce several different clinical pictures.

The viruses capable of causing respiratory tract infection are as follows: influenza viruses, primary atypical pneumonia virus, adenoviruses, infectious pneumonitis of the new-born virus (Sendai, influenza D), Coxsackie A viruses, herpes simplex virus, psittacosis virus, canine distemper virus, unknown virus of common cold, other unidentified viruses. This list is almost certainly incomplete and makes provision for "other unidentified viruses". This is a reflection of the present state of our knowledge. The adenoviruses are interesting. Rowe and others (1953), while growing supposedly sterile adenoid tissue in cultures, observed cytopathic action which they found to be produced by a group of viruses latent in normal adenoids. So far 18 types have been discovered, differing serologically and in pathogenicity, but all are related. They grow best in HeLa cell cultures where they form packed more or less crystalline masses in the cell nucleus.

A study by Evans (1957) of 290 students presenting with upper respiratory tract infections revealed the following infective agents: streptococci, 8·3%; influenza virus, 3·4%; adenovirus, 2·0%; herpes simplex virus, 1·3%; psittacosis virus, 0·3%; unidentified, 83·1%; other bacteria, 1·6%. Notice the high proportion of cases in which the infective agent was unidentified. Most of these, no doubt, were examples of the common cold.

The subject of virus infections of the respiratory tract could have been tackled by classifying the viruses and then describing the diseases they caused, but it is more helpful to approach it the way the clinician would — from the standpoint of a patient with a complaint.

The Upper Respiratory Tract.

The more common infections of the upper respiratory tract which are known or suspected to be of virus origin are acute respiratory disease, non-bacterial pharyngitis, influenza, herpangina and the common cold. These will now be discussed.

[1] Part of a symposium on virus diseases read at a meeting of the Queensland Branch of the British Medical Association on June 6, 1958.

Acute Respiratory Disease.

During World War II a U.S. Commission described the clinical and epidemiological features of undifferentiated acute respiratory disease in recruits. It took the form of an influenza-like respiratory infection that occurred epidemically in the winter months among recruits, but not among seasoned men. One attack seemed to be followed by immunity. The attack consisted of fever, chills, malaise and anorexia, with sore throat, hoarseness and cough. There was moderate pharyngeal redness and hyperplasia, minimal enlargement of the cervical glands and nothing else. The results of laboratory examinations were within normal limits, the duration of acute illness was from three to seven days, and convalescence often required one or two weeks. At that time the ætiological agent could not be isolated by the techniques then available, but filtered secretions of the respiratory tract produced the disease in volunteers, after an incubation period of four or five days. After recovery the volunteers were immune to reinoculation. Further investigation showed that this entity was quite distinct from the common cold and from primary atypical pneumonia.

Ten years later, when the adenoviruses were discovered, antibodies to them were found in the sera of patients convalescent from acute respiratory disease. There was also a correlation between the presence or absence of antibodies and the resistance or susceptibility to infection. It is now accepted that two closely related adenoviruses — types 4 and 7 — cause most cases of acute respiratory disease. This illness has been responsible, over the past 15 years, for over four million cases of patients admitted to hospital in the U.S.A. For some curious reason it is rare in the civilian population and is almost limited to recruit training centres. Preliminary reports on a vaccine prepared from these two strains of adenovirus are most encouraging, giving, in U.S. Army tests, a 98% reduction of naturally occurring acute respiratory disease in recruits.

Non-Bacterial Pharyngitis.

The occurrence of non-bacterial pharyngitis in children has long been noted. In the U.S.A. it has been referred to as "summer sore throat". The disease is usually mild and of short duration with fever, sore throat and injection of the palate, pharyngeal wall and tonsils. The total white cell count remains below 10,000 per cubic mm., and swabbing reveals no pathogenic bacteria.

After the isolation of the new respiratory tract viruses from adenoid tissue, attempts were made to relate them to various diseases, and it was soon found that type 3 adenovirus was connected with outbreaks of non-bacterial pharyngitis. The virus could be isolated from pharyngeal secretions, and neutralizing antibodies to it appeared in the sera of convalescents. Oddly enough, attempts to transmit the disease by intranasal or pharyngeal inoculation of fluid from tissue culture of the virus failed, but transmission was successful via the conjunctiva. Conjunctivitis is a clinical feature in some cases, leading to the designation "pharyngeal-conjunctival fever" by Huebner and the earlier name of "APC viruses" for the group.

In contrast to poliomyelitis, the adenovirus type 3 does not seem to spread widely in a population and is recovered only from patients who are ill. Sub-clinical infections are uncommon.

Influenza.

This is not the occasion to describe in detail the clinical features of virus influenza, which are already well enough known. Few of us have not experienced at some time or other the headache, malaise, general discomfort, muscle pains, prostration and cough with retrosternal soreness. It is also well known that, as in the 1918-19 pandemic, sudden death occasionally occurs even in healthy young adults as early as the second day after the onset of symptoms.

An interesting point recently brought out by Bowden and French (1958) is that the hearts of patients with

fatal cases sometimes show areas of toxic degeneration resembling the toxic myocarditis of diphtheria. They suggest that the presence of these lesions in the heart offers a possible explanation for the suddenness of death, and may be related to the prostration and tachycardia observed clinically in adults suffering from influenza virus infection.

Influenza virus grows readily on the allantoic membrane of the chick embryo, and a number of antigenically different strains have been isolated. The latest polyvalent influenza virus vaccine put out by the Commonwealth Serum Laboratories contains six strains, including last year's type A Asian influenza, and we hope it will prove to be a valuable prophylactic agent.

Herpangina.

The term "herpangina" was introduced by Zahorsky, of St. Louis, who in 1920 described an epidemic febrile disease in children characterized by small numbers of tiny vesicles that progressed to ulcers on the soft palate, anterior pillars and posterior pharyngeal wall. The temperature rose as high as 104° F. with vomiting, anorexia and sore throat, but the disease lasted only a few days and recovery was uneventful. Studies by Huebner and others (1952) have since shown that this illness is caused by several members of the group A Coxsackie viruses. It is not particularly common.

It would be wrong to conclude at this stage that all the causal agents of non-bacterial sore throat have now been identified. Poliomyelitis virus has been found as an infecting agent in studies of what were thought to be respiratory infections, and herpes simplex virus has been found even in the absence of herpetic mucous membrane lesions, and I believe that any virologist would be ready to admit that there must still exist some, if not many, undiscovered virus agents.

The Common Cold.

Laymen have always considered the common cold to be a standing joke against the medical profession. It must be admitted that they have something in their favour. Gohd (1954), in a recent comprehensive report, declared: "One cannot escape the conclusion that progress in the understanding of the common cold has not been conspicuous."

All the same, a certain amount of information is available, mainly from volunteer studies made under rigid conditions of isolation to eliminate extraneous infection. There is no doubt that filtered, bacteria-free secretions will transmit the disease to volunteers, that the agent is therefore a virus, and that bacteria are not required for the initiation of the illness. A susceptible host other than man and chimpanzee has not been found, and as yet there has been no confirmed success in laboratory cultivation of the virus. The most promising report so far is that of Andrewes and others, who in 1953 managed to propagate common cold virus through ten serial cultures of embryonic human lung. Virus could not be detected beyond the tenth serial passage, and it is not known whether it was lost or became attenuated on the way.

It is hard to over-estimate the importance of the common cold, regarded by some virologists as being responsible for approximately 40% of all illnesses (Dingle and Feller, 1956). Writers emphasize the special difficulties of its study. For example, antibody production is evidently inadequate and brief, there are no susceptible animals for experimental purposes and the virus cannot be persuaded to grow in the laboratory. Thus laboratory confirmation of a clinical diagnosis is impossible. We can disagree with those who say that clinical diagnosis is uncertain, that it depends on subjective criteria and that differentiation from hay-fever and vasomotor rhinitis is not easy. The true common cold has a particular sequence not hard to recognize. It commences with a sore throat, which progresses to nasopharyngitis with a raw feeling behind the nose, and then acute rhinitis with watery discharge in which one side may precede the other by several hours. This is followed by pansinusitis with mucopurulent discharge and finally by a descending tracheitis and cough. In this form it is a fairly clear-cut clinical entity. But the causal agent has yet to be found.

The Lungs.

Virus infections of the lungs are influenzal pneumonia, primary atypical pneumonia, virus pneumonitis of the new-born, psittacosis and canine distemper. Influenzal pneumonia is included simply to stress the fact that influenza virus infections are liable to involve the entire respiratory tract and will not be further discussed.

Primary Atypical Pneumonia.

It is twenty years since clinicians first recognized the disease that came to be called "primary atypical pneumonia". It differed from the ordinary pneumonias in that pathogenic bacteria could not be isolated from the respiratory tract and in its failure to respond to sulphonamides. X-ray evidence of lung involvement was rather characteristic in its distribution and out of proportion to the physical signs, which could even be absent. Cough was persistent and troublesome, but dyspnœa uncommon and cyanosis rare. Confirmation of the diagnosis depended upon the discovery of a normal leucocyte count and the development of a high titre of cold agglutinins against group O human erythrocytes.

Primary atypical pneumonia remained a disease of unknown ætiology until 1944 when Eaton isolated from patients with the disease a virus which grew on chick embyro and took up antibody in convalescent serum by the fluorescent antibody technique.

Experts now recognize at least four strains of this virus, which cause pneumonia in cotton rats and can be neutralized by human convalescent serum. Patients who are recovering develop antibody between the second and third weeks of illness. All of the 27 cases in a certain recent school epidemic of primary atypical pneumonia developed antibody to Eaton's virus and most of these had cold agglutinins. There was no crossing with adenoviruses or the causative agents of influenza, psittacosis or "Q" fever.

However, it is evident that primary atypical pneumonia is a syndrome of multiple ætiology. For instance, Adams (1953) has called attention to the similarity between the pathological lesions of canine distemper and those of humans with primary pneumonitis, and he has recorded the cases of two children with pneumonitis who developed antibodies to distemper virus in the course of their illness. One child became sick ten days after the death of his puppy from distemper. It has recently been shown that antibodies to canine distemper are widespread in adult human populations.

Psittacosis.

Psittacosis achieved prominence in 1929-30 when an epidemic involved 750 to 800 persons in 12 countries. For some reason clinical infection is rare in children. Almost all cases arise from contact with infected birds. The principal pathologic finding in fatal cases is patchy bronchopneumonia, polymorphonuclear leucocytes being absent from the exudate. The onset of the illness, after an incubation period of about ten days, is gradual, with chilly sensations and rising temperature. Photophobia, headache and dry cough are usually noted, and epistaxis is common. Observers are impressed with the toxic appearance of the patient, and the resemblance to typhoid fever is striking. In early cases physical signs of pneumonia are lacking, but later suppressed and altered breath sounds and sticky rales may be noted. It has always surprised me that psittacosis is so rare in Australia, considering how many families keep budgerigars as pets and the frequency with which the disease has been traced to imported Australian budgerigars in other countries.

Virus Pneumonitis in the New-Born.

In 1952 a severe outbreak of pneumonitis occurred in a nursery for new-born babies at Sendai in Japan. Eleven

of 17 affected babies died. The illness had an abrupt onset with fever, dyspnœa and cyanosis. Physical signs were minimal until shortly before death, but X-ray examination showed extensive changes with diffuse shadows in the lungs. At autopsy intensely hyperæmic lungs with foci of hæmorrhagic pneumonia were found.

Bacteria-free filtrates of lung tissue produced similar changes when inoculated intranasally into mice. The new virus had influenza-like qualities, but was not neuralized by antisera to the known strains A, A^1, B or C. It has been suggested that this virus should be called "influenza D" instead of "new-born pneumonitis virus, type Sendai". More recent studies have shown it capable of causing a moderately severe pneumonia in an older child. It is present in the population both in the U.S.A. and in Great Britain, where it seems to have been associated with primary atypical pneumonia and with an influenza-like illness.

To conclude this short survey, the following list is presented of the conditions that have been described, together with the presumed infective agents. It summarizes our knowledge at the present time, but no doubt within a few years it will be regarded as shockingly incomplete. Even now I suspect that it makes the subject much too tidy and far too simple.

I. Acute respiratory disease—adenovirus types 4 and 7.
   Non-bacterial pharyngitis—adenovirus type 3.
   Influenza—influenza viruses (various strains).
   Herpangina—Coxsackie A virus.
   Common cold—unknown virus.

II. Influenzal pneumonia—influenza viruses.
   Primary atypical pneumonia—primary atypical pneumonia virus.
   Virus pneumonitis of the new-born—influenza D (Sendai).
   Psittacosis—psittacosis virus.
   Canine distemper—canine distemper virus.

In all that has been said there has been no word of treatment, for the good reason that no specific treatment, other than prophylaxis, is yet available. Whether it will ever be possible to develop chemical agents that destroy viruses inside body cells, without at the same time destroying those cells, remains to be seen.

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Reviews.

Human Dissection: Its Drama and Struggle. By A. M. Lassek, M.D., Ph.D.; 1958. Springfield, Illinois, U.S.A.: Charles C. Thomas, Publisher. 9" × 5¾", pp. 320, with 13 illustrations. Price: 50s.

THE story of the history of anatomy is a fascinating subject, and one which has claimed the attention of many authors, particularly in this century. A number of authors have dealt with the vital aspect of the supply of anatomical subjects for the purpose of dissection; this, prior to the passing of the *Anatomy Act* in 1832, was haphazard, fraught with many illegal practices and clouded by the activities of the resurrectionists. Even today, so long after the passing of the necessary legislation, it is a matter of concern to all schools of anatomy.

Previous authors have given us authoritative and well-written accounts of the history of anatomical dissection, but the same cannot be said of the book under review. It is a most pedestrian work, whose only value lies in the account given of anatomical dissection in America, although some aspects of this have been better covered by other writers.

Dr. Lassek would appear to be reluctant to quote from primary sources—a characteristic which reaches absurd proportions on page 172, when he quotes the Lord Chief Justice's sentence on the notorious William Burke from a recent journal article instead of from the official account of the trial; plenty of other examples could be given.

With a great wealth of historical illustrations at his disposal, the author is content to borrow many of his plates from J. M. Ball's "The Sack-em-up Men"; indeed, all his plates have been previously published in books and journals and are used with acknowledgement to the original author. The text contains a number of minor inaccuracies. On page 142 there is obvious confusion between John and William Hunter in regard to their life and work. It should be pointed out, too, that the gubernaculum testis was described by John and not William.

Throughout the text there is emphasis on the sensational, and the quality of writing varies considerably. Should a reader require a critical, well-balanced and well-documented review of the history of anatomical dissection and the supply of anatomical subjects he will not get it in this book. The publishers claim that the book "brings the great mass of knowledge regarding the role of human dissection in the medical profession into a coherent, historical perspective". It is a matter for regret that the author fails to do this.

Baby and Child Care. By Dr. Benjamin Spock; Second Edition; 1958. London: The Bodley Head. Melbourne: William Heinemann, Limited. 7¼" × 4¾", pp. 608, with illustrations. Price: 18s. 9d.

THE genius of Benjamin Spock, whose famous book on "Baby and Child Care" has now appeared in a new and enlarged edition, is that he gives an adequate and sensible answer in simple language to almost every question that can possibly be posed on the subject of child management. His acute sensitivity to the reactions of parents leads him to apologize, on the opening page, to those who have girls and are frustrated by having the child called "him" throughout the book. He warns them also against taking too literally what they will read, as every child, every parent and every behaviour problem is somewhat different from all others.

As before, the book is divided into numbered sections—nearly eight hundred in all—well indexed and classified with intriguing titles such as: "Glandular Disturbances"; "The Child Who Can't Eat Breakfast Before Going to School"; "How to Handle Different Kinds of Jealousy"; "Why Does an Older Child Lie?" Arranged in this form, the book may sound somewhat jerky, but it is really not so. The material is grouped in chapters under general headings such as feeding, illness, managing young children, etc., and special problems are dealt with according to age groups. In any case, it is a book to be kept handy and dipped into, rather than read straight through.

The section on twins has been much enlarged as a result of 200 letters from mothers of twins describing how they mastered their problems. Various short cuts are advised—for example, that "bathing can be skimped a great deal if care is taken", and "it may not seem hygienic or polite to use only one dish and one spoon, but it's so much more practical".

One is constantly struck by the author's simple common sense. He is no perfectionist, and writes only of what parents may reasonably be expected to do. For example, speaking of accidents, he admits: "Parents cannot prevent all accidents. If they were careful enough or worried enough to try, they would only make a child timid and dependent."

Reference is made to the fact that, when the first edition was being written 15 years ago, the attitude of most people towards infant feeding, toilet training and child management was still fairly strict and inflexible. The author, in common with most pædiatricians and child psychologists, was at that stage trying to urge greater understanding

of the child and greater flexibility. Since then, the change of attitude has been so great (probably more in the U.S.A. than in Australia) that there now seems more chance of a conscientious parent's getting into trouble with permissiveness than with strictness. We find Spock, therefore, urging reasonable attempts at easing the baby into a four-hourly feeding timetable after an initial period of demand feeding. After all, "she doesn't have to prove she is a good mother by ignoring her own convenience". Parents are told quite plainly that they need not go on being sweetly reasonable for ever—that children expect to be corrected, and are happier as well as better behaved if the parents insist on reasonable standards of conduct.

In line with the general simplification of infant feeding that has taken place in many countries, we notice a great reduction in the number and variety of formulæ recommended. Whereas there were 22 in the first edition (11 each for evaporated milk and whole-milk dilutions), there are now two only, both made on evaporated milk, a moderately dilute formula for new-born babies and a standard formula for babies weighing 10 pounds and upwards.

This is an excellent book, though not strictly a medical book, being intended mainly for parents. We urge all doctors to buy it. It is likely to become so popular with the young mothers in the newer suburbs, where the babies are, that one can hardly imagine a medical graduate having the effrontery to commence practice there without having first read his Spock.

Notes on Books.

Progress in Clinical Psychology. Edited by Daniel Brower, Ph.D., and Lawrence E. Abt, Ph.D.; Volume III, 1958. London and New York: Grune and Stratton, Incorporated. 9″ × 5½″, pp. 256. Price: $7.75.

THIS volume, like its predecessors, "attempts a systematic and critical look at the contemporary scene in clinical psychology particularly during the past two years". It consists of 16 chapters contributed by American consulting and other psychologists. After two introductory chapters, the next seven comprise a symposium on "The Psychodiagnostic Test Battery". Part III consists of nine chapters under the collective heading of "Changing Conceptions in Psychotherapy". The final chapter is entitled "Clinical Psychology in Other Lands". The approach throughout this volume is essentially a practical one, and, broadly, the first half of the book is devoted to the practical aspects of psychodiagnosis, and the second half to the practical aspects of psychotherapy. A chapter on "Mysticism and Psychoanalysis" by Bernard Walstein deals with more basic issues than most of the others, and is regarded by the editors as a signally important contribution. The long lists of references at the end of each chapter should prove a valuable feature.

Industry and Tropical Health III. Proceeding of the Third Conference of the Industrial Council for Tropical Health, sponsored by the Harvard School of Public Health, April 16-18, 1957, in Boston. Published for the Industrial Council for Tropical Health by the Harvard School of Public Health, Boston; 1957. 10½″ × 7½″, pp. 264, with many illustrations. Price $10.

THE participators in these conferences are medical directors of leading American corporations with extensive commitments in tropical countries, and leading authorities on tropical medicine and hygiene. This volume consists of the papers, mainly short, submitted to the third conference, together with the accompanying discussions. A wide variety of subjects are covered, and the papers are of general rather than of specialist interest. Many of the papers are informative, but they appear to contain little that is strictly original, and they are chiefly intended as authoritative discussions of problems confronting the industrial medical officer in the tropics.

Pharmacological and Chemical Synonyms: A Collection of More than 8000 Names of Drugs etc. from the Medical Literature of the World. Compiled by E. E. J. Marler, M.D., M.Sc., Ph.D.; Second Edition; 1958. Amsterdam, New York: Excerpta Medica Foundation. 9½″ × 6½″, pp. 176. Price not stated.

THIS is an alphabetical list of names for drugs and other substances of pharmacological or biochemical interest, and is the second edition of an index originally developed as a key to the subject under the section on "Pharmacology, Biochemistry and Physiology" of *Excerpta Medica*. The list contains a collection of more than 8000 names, and is completely cross-indexed, so that each substance is listed under its correct chemical name (special attention has been paid to the use of systematic chemical nomenclature on the model of the leading chemical abstracting journal), its abbreviated chemical name, its official name(s), and its trade or other name(s), each entry referring to the primary heading, which is the correct chemical name, and under which are listed all the alternative names. British spelling is used throughout. The editor modestly states that the list makes no claim to be either official or complete, but in fact the list appears to be remarkably comprehensive, and the compiler is to be congratulated on producing a list which should prove invaluable to all those who need a ready means of identifying the many new substances which appear in the medical literature, under a bewildering variety of names, and a guide to the status of these various names. It should be noted that the division into two separate lists used in the first edition has been abandoned, and the present edition is arranged as a single comprehensive list.

Cerebral Vascular Diseases. Transactions of the Second Conference Held under the Auspices of the American Heart Association, Princeton, New Jersey, January 16-18, 1957. Chairman, Irving S. Wright; Editor, Clark H. Hillikan. 1958. New York and London: Grune and Stratton, Incorporated. 10″ × 6½″, pp. 232, with illustrations. Price: $4.00.

THIS volume presents the transactions of the second conference on cerebral vascular diseases, held under the auspices of the American Heart Association in January, 1957. Each chapter consists of a short paper on some topic followed by a verbatim account of the discussion which followed. Some papers are on experimental topics, such as the estimation of cerebral blood flow. Chapters of more general clinical interest include those on the relationship of hypertensive vascular disease, intermittent cerebral ischæmia, the therapy of atherosclerotic disease, and anticoagulant therapy in the treatment of cerebral thrombosis. Neurosurgery is represented by a paper by E. H. Botterel on surgical aspects of hæmorrhage from intracranial aneurysm. A committee report entitled "A Classification and Outline of Cerebro-Vascular Diseases", reprinted from *Neurology*, May, 1958, is included at the back of the volume.

Side Effects of Drugs: Untoward Effects of Drugs as Reported in the Medical Literature of the World during the Period 1956-1957. Compiled by L. Meyler, M.D.; 1958. Amsterdam, New York: The Excerpta Medica Foundation. 9½″ × 6½″, pp. 194. Price not stated.

THE object of this volume is to present a synopsis of the undesirable side effects produced by medicinal drugs of all kinds, reported during the period 1956-1957. A previous volume (the first edition) covered the period 1955-1956, and reports noted in that edition are not repeated in the present volume. However, this volume contains a cumulative index referring to both. The index contains some 2500 entries, though many of these are synonyms. There are 28 chapters, each dealing with some group of drugs; under each drug mentioned is given a synopsis of the side effects reported; in many instances this takes the form of brief reports of cases; at the end of the chapter is a list of the relevant references. Neither titles nor authors' names are quoted. This volume is a reminder that few drugs are entirely free from the risk of adverse side effects; but its real value is as a work of reference, and it could be usefully consulted by anyone wishing to report on or discuss any adverse effects of drugs occurring in his own practice, or by anyone in any other way interested in the subject.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Trends in Leprosy in the Pacific: An Account of the Introduction and Spread of Leprosy in the Pacific, and of its Importance in Pacific Health", by D. A. Lonie. Technical Information Circular No. 32; 1959. Noumea and New Caledonia: South Pacific Commission. 10½″ × 8″, pp. 34. Price: not stated.

A summary of the known history of leprosy in the Pacific area, and of its current prevalence.

The Medical Journal of Australia

SATURDAY, JULY 25, 1959.

SEX AND NUCLEAR SEX.

THE discovery of nuclear sexing illustrates a common trend in science—namely, that the first application of a new technique brings forth a wave of enthusiasm. This leads to numerous disjointed reports, which in turn leave in their wake confusion where order previously reigned. However, further experience and sober reflection show that the previous order was more apparent than real, and that the confusion can eventually be put right. At the present time we are at the stage of confusion in the matter of nuclear sexing.

In 1949 Professor M. L. Barr showed that it was possible to detect sexual dimorphism in the nuclei of certain cells of the central nervous system. The use of resting cells freed the geneticist from the need for using cells involved in active division and so paved the way for clinical application. In general terms, the distinction between male and female nuclei lies in the detection of sex chromatin in the nuclei of female cells and its absence from the nuclei of male cells. It is important to remember that the significance of sex chromatin is not clear, but that its presence is in some way related to the occurrence of XX sex chromosomal configuration. At the same time, all female cells do not contain sex chromatin, and all male cells do not lack it. In fact the proportion of cells showing such chromatin is far from the expected value, because all the cells of an organism are supposed to be of the same genetic constitution. The proportion of chromatin-positive cells encountered is not fixed for males or for females and varies greatly from tissue to tissue. Although these confusing observations do not prevent the successful use of the empirically observed preponderance of chromatin-positive cells in females, they are likely to remain obscure until more is known about the true nature of the sex chromatin.

On the tricky question of nomenclature, it would be prudent at the present stage of our knowledge to show great caution, and those who intend to coin new names will do well to be circumspect in their choice. It seems wise to avoid, for example, terms which suggest a relationship between female genetic sex and femininity—e.g., "female nucleus", "female chromosomal sex", etc. We are uncertain of the true significance of sex chromatin, and femininity (or "femaleness") involves somatic and psychological considerations not immediately relevant to genetic patterns. The term "skin sex" has been abandoned since the technique has been applied more generally, and although the expressions "nuclear sex" and "chromosomal sex" are unexceptionable, the more precise terms "chromatin-positive" (for female cells) and "chromatin-negative" (for male cells) are to be preferred. The sex chromatin itself consists of a small mass of chromatin seen within the nucleus. It may form a single spherical mass; or with better preparations it is sometimes seen to consist of two portions (diplococcus form), and vacuoles, spiral forms and shapes suggesting the letters "M" and "S" have all been described. The sex chromatin has been given several names. The term "drumstick" is only crudely descriptive, while "nucleolar satellite" suggests other branches of science. The choice would seem to lie between "chromocentre" and "chromatin body"; of these the latter is preferred because it is less esoteric. These considerations necessitate a number of adjectives to qualify the sex of an individual. The genetic sex or genotype refers to the nature and number of sex chromosomes in the somatic cells of an individual (normally XX or XY). The phenotypic sex or phenotype refers to the apparent somatic sex, i.e., the nature of the internal and external genitalia. The legal sex refers to the sex registered at birth; the nursery sex refers to the sex adopted at birth under the influence of the parents; while the psychological sex refers to the emotional orientation of an individual with regard to members of either sex.

The nature of the chromatin body is undecided, although an increasing body of evidence favours the view that it represents fusion of the heterochromatic portions of the two X chromosome. Other suggestions include the view that the chromatin body represents extrachromosomal chromatin which is a secondary sexual characteristic. Again, it has been suggested that variations in the number of chromosomes in the various cells of the body may be responsible for the presence of the chromatin body. With better technique it appears that the proportion of cells which are chromatin-positive in female tissue and the proportion of cells which are chromatin-negative in male tissue in each case approaches 100%. It is evident that the XX configuration is necessary for the appearance of sex chromatin, but its absence from certain tissues remains to be explained.

It will be recalled that sex determination is believed to take place at the time of fertilization and is decided by the nature of the sex chromosomes in the fertilizing spermatozoon. Sex differentiation refers to the morphological changes in the gonads, genital ducts and external genitalia which lead to male or female forms. The genetic constitution influences these changes in this order. The gonad is originally bisexual and consists of a cortex and a medulla. XX genetic constitution facilitates cortical development, which results in the formation of an ovary, while XY constitution facilitates medullary development with the formation of a testis. Medullary development is associated with the production of some humoral substance which promotes development of the

genital ducts in a male direction. The development of female genital ducts appears to be autonomous and proceeds in the absence of gonadal influences; in this respect the influence of the fœtal testis is homolateral, affecting only the duct of the same side. If one component of the indifferent gonad is suppressed, the other component develops regardless of the genetic constitution of the host.

These observations are of more than academic interest. Nuclear sexing has proved to be of considerable value in the diagnosis of certain conditions involving doubt about the true sex of those affected and of inestimable value in accounting for the pathogenesis of these and allied disorders commonly referred to as disorders of sex. A fuller discussion of these would be warranted on another occasion. In addition, the information obtained from these studies has led to a better understanding of the mechanism by which genetic factors affect human development.

Current Comment.

SWIMMING POOLS.

WATER has a fascination for young people of all ages up to ninety. In countries like Australia, with an equable climate and much sunshine, swimming is a national pastime. There are endless opportunities for pursuing it, not only on the coast, where so many excellent beaches are to be found, but also in inland rivers and creeks. However, none of these places are without their dangers, and in every season there are one or two fatalities. These are not by any means always due to the victim's inability to swim; they may be caused by the natural hazards of the place in which he is swimming. The excellent work done during the school holidays in teaching the children to swim must have by now reduced very considerably the proportion of the population who cannot swim. The importance of learning to swim is highlighted by an article entitled "Artificial Swimming Pools" by H. F. Hustler.[1] In this he draws attention to what he describes as some intrinsic problems associated with the building of an artificial pool. In presenting the case for the artificial pool, Hustler refers to its safety as compared with natural waters. He states that in such bathing places as rivers and creeks there may be irregular depths, submerged stumps, weeds to entangle swimmers, and opacity of water which will hide a submerged person from view. Moreover, drain water and effluents enter natural waters, and for non-swimmers beaches with surf and undertow are dangerous. A well-built modern pool is almost an essential for teaching pupils to swim, and also for competitive swimming of standards such as those observed in the Olympic Games. From the sociological point of view, the swimming pool has an attraction for young people, and it has been observed that there is little larrikinism amongst youngsters enjoying its facilities and its pleasant surroundings.

Hustler presents an interesting summary of present knowledge of structural problems, water treatment, sterilization, alkalinity and algæ. This would well repay reading by any who are interested in the construction of a pool. However, in this place the greatest interest lies in his discussion of the medical and bacteriological aspects of swimming pools. He refers to an article by N. J. Martin reprinted from the report of the twenty-fourth annual conference of the Health Inspectors' Association of New South Wales, in which a bathing load of 20 person per 1000 gallons—that is, 50 gallons per person—is recommended. Hustler points out that the bathing load should not be allowed to become so great as to disturb the clarity, the bacterial condition and the chlorine residual of the water. Most of the bacteria added to the water by bathers are harmless. Some cause disease, but in a well-conducted pool their numbers should be negligible. There is a greater risk of infection from overcrowding of the pool and the dressing-room and from the sharing of towels or swimming costumes. Some interesting facts on the transmission of infection by the water of swimming pools are taken from a publication of the British Ministry of Health (1951) on the purification of the water of swimming-baths. In summary, these are as follows. Gastro-intestinal infections are seldom transmitted by swimming-bath water. Skin infections are more likely to have been transmitted by towels, swimming suits and seats than by the water. Inflammation of the ear appears generally to be due to the swelling of wax and skin casts by the water. Erythema and rashes due to the chemicals used for water purification should not occur in a properly managed pool. Conjunctivitis does sometimes result from the chemicals used in swimming-bath water, but it is more commonly spread by towels. Nasopharyngeal and respiratory infections may easily be spread in crowded baths, corridors, dressing-rooms and cubicles. Infections may be contracted by contact with carriers outside the water, and the subsequent occurrence of disease may be determined, among other things, by lowered resistance from fatigue and chilling due to too long immersion in cool water. To prevent air-borne infections, there must be proper ventilation of the bathing-hall, and overcrowding should be avoided. With regard to otitis media, an investigation was carried out over a period of ten years at Guy's Hospital into the types of organisms causing the condition. It was found that in the acute disease the infecting bacteria were nearly always hæmolytic streptococci whatever the clinical picture; occasionally pneumococci were found, and more rarely Friedländer's bacillus and *Bacterium coli*. The conclusion reached was that hæmolytic streptococci and pneumococci were the principal organisms involved. There have been only a very few records of the recovery of hæmolytic streptococci and pneumococci from swimming-bath water. In chronic otitis media the responsible organisms were the same as those of the skin and therefore of polluted swimming-bath water. The comment made on this condition is that the possibility that harm will be done by bathing to a person with established chronic otitis media is minute in comparison with the mental trauma inflicted on a young person who is prohibited from bathing, so that a distinction is made between him and other children. This viewpoint is perhaps open to question on a number of grounds: (*a*) in the present state of knowledge "running ears" are nearly always amenable to treatment; (*b*) patients under treatment for middle-ear disease should not be allowed to swim without the express permission of their medical advisers; (*c*) "dry" perforations are frequently reinfected by bathing—such patients should not swim unless their ears are protected by properly fitting plugs; (*d*) the presence of people with infective discharges of any kind in public swimming pools is offensive to our sense of hygiene and should not be encouraged. Finally, with regard to poliomyelitis, it is considered that at times of high incidence, the balance of evidence favours the keeping open of public baths and swimming-pools provided that they are properly conducted. Special attention should be given to the prevention of overcrowding both in and out of the water, to the effective laundering and sterilizing of towels and swimming costumes, and to the thorough cleansing and disinfecting of all dressing-sheds and toilets.

Summarizing the position, Hustler states that more and more people are using swimming pools. If these pools are untreated, they can have an adverse effect on public health, but if they are properly constructed and controlled, they may have something to contribute to the physical and mental health of the public, in particular

[1] *Good Health for South Australia*, 1958 (July).

of the younger generation. The provision of healthy and attractive swimming-pools is to be encouraged; but the provision of concrete holes filled with raw water lacking proper supervision of construction or water treatment is likely to be damaging to health and is not the correct answer.

NITROGLYCERIN AND THE CORONARY CIRCULATION.

NITROGLYCERIN remains the most satisfactory drug for the systemic treatment of coronary disease of the heart, but its mode of action is still not clear. When Sir Lauder Brunton introduced it in 1867 he attributed the clinical effect of the drug to the initiation of peripheral vasodilatation with consequent lowering of peripheral blood pressure. It was later shown that the vasodilatation affected also the coronary vessels. At the present time the peripheral effect is not usually considered of much importance. Recently a group of workers at the Harvard Medical School has studied the effect of nitroglycerin on the coronary circulation of normal or nearly normal subjects and on subjects with coronary artery disease or increased left ventricular work. N. Brachfeld, J. Bozer and R. Gorlin[1] studied the effect in normal subjects and R. Gorlin, N. Brachfeld, C. MacLeod and P. Bopp[2] the effect in patients with heart disease. Patients were studied by cardiac catheterization. In the normal and near normal series ten subjects were studied, six of whom had minor cardiac defects not related to coronary disease, and in the heart disease series 17 patients were studied. Seven patients had coronary sclerosis and angina pectoris; ten had various degrees of cardiac deficiency, and of these seven had angina pectoris. Observations of coronary and systemic circulatory dynamics and myocardial gaseous metabolism were made before and after the administration of nitroglycerin. In the normal group the amount of myocardial oxygen was increased during the administration of nitroglycerin. Coronary blood flow increased by 63%, while the oxygen extraction remained unchanged. This increase in oxygen utilization is not surprising in view of the known effect of nitrites on oxygen utilization by cells. The increase in coronary blood flow was due to a lowered coronary vascular resistance. The increase in myocardial metabolism was associated with unchanged cardiac work and a fall in myocardial efficiency. Blood pressures diminished very little in these subjects after administration of nitroglycerin.

The patients with heart disease were studied in the same way. In these subjects administration of nitroglycerin resulted in a decrease in cardiac output, blood pressure and left ventricular work, with a fall in systemic and pulmonary venous pressures. An interesting point is that coronary vascular resistance was normal before administration of nitroglycerin and remained essentially the same afterwards. The same thing occurred with the coronary flow and myocardial oxygen consumption, and the efficiency fell. There is thus a difference in reactivity between the normal and diseased coronary circulation which may be related to a prior exhaustion of the available vasodilator capacity of the heart, either by intrinsic coronary arterial obstruction or through hæmodynamic overloading of the left ventricle by disease. An explanation for the relief of pain in angina pectoris by nitroglycerin is not apparent in view of the findings noted. Nitroglycerin may produce its effect in relieving pain by decreasing the contractability of the heart muscle rather than by relaxing the coronary vascular tree.

P. C. Gazes, J. A. Richardson and E. F. Woods[3] in a study on the plasma catechol amine concentrations in myocardial infarction and angina pectoris have come to a similar conclusion—that they probably act largely by reducing peripheral resistance and thus reducing the weight load of the heart. These authors found that the concentration of noradrenaline was significantly increased in the blood in many cases of myocardial infarction and in cases of angina pectoris after exercise. Adrenaline levels were increased in a small number of cases. Of the concentration of amines in the myocardium 75% to 90% consists of noradrenaline, in contrast to the ratio in the adrenal medullary secretion. Gazes and his colleagues consider that a considerable amount of noradrenaline comes from the myocardium in myocardial infarction and angina pectoris after exercise. There is reason to believe that these amines intensify anginal pain, so it is rational therapy to reduce the output from the adrenals by physical rest and mental relaxation, and by avoidance of cold, heavy meals and excessive tobacco smoking. Nitroglycerin may have a specific anti-adrenergic action on the heart, as has been suggested by W. Raab and E. Lepeschkin.[1]

[1] *Circulation*, 1959, 19:697 (May).
[2] *Circulation*, 1959, 19:705 (May).
[3] *Circulation*, 1959, 19:657 (May).

METABOLIC CARBON MONOXIDE IN MAN AND SEALS.

J. S. HALDANE in his investigations on blood volume and on oxygen tension of arterial blood assumed that the source of carbon monoxide in the blood could only be the air admitted into the lungs, and further, that there was no method of disappearance other than by the pulmonary path. In a study of carbon monoxide levels in man living at Scott Base, Antarctica, reported by L. G. C. E. Pugh,[2] it was found by chance that the blood of a Weddell seal contained as much carbon monoxide as the blood of men who were heavy smokers. That the active volcano, Erebus, might supply this was considered and ruled out, as also was the suggestion that it might originate from the ooze on the sea bed. Further investigation pointed clearly to the finding that this carbon monoxide was produced when hæmoglobin disintegrated into bile pigment. This metabolic origin of carbon monoxide must be borne in mind when the presence of carboxyhæmoglobin in human or other blood is accepted as indicating an exogenous origin from smoking or from breathing air tainted with products of incomplete combustion of fuel, gas or oil. At the same time it should not be forgotten that the respiratory physiology of seals is adapted to spending long periods completely submerged. One reflection of this adaptation is the fact that the hæmoglobin value of seal blood is over 20 grammes per 100 millilitres.

[1] *Circulation*, 1950, 1:733 (April, Part 2).
[2] *Nature*, 1959, 183:74 (January 10).

"SWOPS."

A MEDICAL PRACTITIONER from Tasmania has recently made an interesting suggestion. He points out in a letter that it frequently happens, especially in Tasmania, but probably also in other States, that a doctor intends to visit another State and would like to have a car available at a minimal cost. Occasionally it is possible to arrange a "swop" of cars and even of houses, but it is difficult to make contact with the right person at the right time. In the light of this the Tasmania doctor suggests that the Journal might well run a free "swop" section for the benefit of members who are thinking of doing as he mentions. We think that this is a good idea and shall be glad to cooperate. Those interested could advise us of the dates on which they intended to travel, whether or not they wished to "swop" cars or houses or both, and the exact dates for which they wished the "swop" to be effected. "Swops" would be published in the "Notes and News" section. The Journal could not of course accept any responsibility in the matter, and we should need to know the details at least two weeks before the date on which publication was desired.

Abstracts from Medical Literature.

PATHOLOGY.

Tumour Cells in Bone Marrow and Blood.

A. A. SANDBERG *et alii* (*Cancer*, November-December, 1958) examined the blood of 600 patients who were selected because of an established or presumed diagnosis of cancer. The frequency of cancer cells in the bone marrow was approximately 8%. In 305 patients both sternal aspirations and blood samples were screened for the presence of tumour cells. There were 22 patients with positive findings in the marrow and 27 with tumour cells in the blood; in only six of these patients were tumour cells found in both bone marrow and blood. Tumour cells were found in seven patients who had no evidence of metastases; in five of these the cells were found in the marrow, and in two they were in the blood.

Transfusional Siderosis.

R. A. M. OLIVER (*J. Path. Bact.*, January, 1959) has studied 22 patients who had received more than 30 pints of blood. A mild form of hæmochromatosis developed in a proportion of patients receiving more than 40 pints of blood, whilst those who had received more than 120 pints all showed skin pigmentation and pancreatic siderosis, with glycosuria and hepatic fibrosis in the majority. It did not appear that siderosis caused significant alteration in cardiac function, in hepatic function or in the course of the disease. Transfusional siderosis differs from idiopathic hæmochromatosis in the large amount of iron found in the spleen and reticulo-endothelial system, in addition to the liver. Quantitative estimation of iron in the liver in six cases showed concentrations of iron comparable to those in idiopathic hæmochromatosis, but macroscopic cirrhosis was not found. In some cases an increase of periportal fibrous tissue was found. The relation of transfusion siderosis to other forms of generalized siderosis is discussed. In addition to transfused blood, dietetic factors, hæmolysis and a hypercellular bone marrow seem to predispose to siderosis. Hepatic fibrosis is an essential feature of all types of hæmochromatosis. It is postulated that evidence of tissue damage such as cirrhosis is not found until the excessive iron load has been present for 40 to 50 years, hence the mildness of the changes in transfusional siderosis.

Gynæcomastia.

N. TREVES (*Cancer*, November-December, 1958) has analysed the condition of breast hypertrophy in 406 cases of simple gynæcomastia, 525 cases of testicular tumour and 13 examples of adrenal neoplasm. Gynæcomastia was found to occur predominantly during puberty and adolescence, with a second highest incidence during the time of "male climacteric". The lesion was predominantly unilateral except when produced by testicular or adrenal neoplasms. The location of the mass was usually central, in contrast to the position of male breast cancer, which is usually eccentric. Nipple abnormality was rare. Endocrine disorders were found in 24% of these patients; they included general endocrine imbalance, and pituitary, thyroid, testicular and prostatic disorders. In no case did breast cancer supervene. In patients with testicular tumours there was a 10% incidence of gynæcomastia, and a similar incidence in association with benign testicular abnormalities. When associated with malignant testicular neoplasms, gynæcomastia was usually bilateral and irreversible. Two hundred and sixty of the 406 patients with simple gynæcomastia were followed adequately. There were 136 patients who received no treatment, and amongst these there was complete clinical regression in 115 (85%). Satisfactory results were obtained in 117 (94%) of the patients who received treatment; this consisted of surgery, or the administration of testosterone, or both. The cause of gynæcomastia is thought to be endocrine imbalance in the majority of cases, but other factors playing a part are nutritional deficiencies, administration of œstrogens or androgen, liver disease and testicular, adrenal or hypophyseal tumours. Although gynæcomastia is usually the manifestation of some benign condition and will often regress spontaneously, its presence should always stimulate a search for more serious causes, especially when it is bilateral.

Klinefelter's Syndrome.

J. R. AUGUSTINE AND Z. F. JAWORSKI (*A.M.A. Arch. Path.*, August, 1958) have recorded an unusual example of "true" Klinefelter's syndrome in which, at autopsy, there was found to be complete absence of interstitial cells in the testes. This is ascribed to the coexistence of cirrhosis of the liver.

Late Effects of Total-Body Irradiation.

B. G. LAMSON *et alii* (*A.M.A. Arch. Path.*, September, 1958) irradiated rats during the maintenance of a hypoxic state. They were given 1000*r* total body irradiation, which was equivalent to a dose in the vicinity of 500*r* under normal atmospheric conditions and represented a figure between 71% and 83% of an LD_{50}. This amount of irradiation retarded growth of the animals and reduced their life span by nearly 40%. Cataracts appeared much earlier, and some rats developed bilateral nephrosclerosis, a condition not seen in the controls. Large pituitary adenomata were common in the controls but absent in the irradiated animals. Tumours as a whole were no more frequent in irradiated animals, although ovarian tumours seemed to be specifically increased. In general, the main effect of the irradiation was an acceleration of the aging process of the animals, in this way hastening the appearance of the usual diseases common in aged rats, namely cataracts, susceptibility to acute inflammations, epilation and skin ulcerations.

B. G. LAMSON *et alii* (*A.M.A. Arch. Path.*, September, 1958) studied the hypertension and nephrosclerosis produced in rats surviving 1000*r* hypoxic total-body irradiation. The authors found that the blood pressure was consistently raised in the survivors. Nephrosclerosis was due to the hypertension and was not an irradiation effect. It did not differ from nephrosclerosis accompanying hypertension produced by other means.

Experimental Dietary Siderosis.

T. GILLMAN, M. HATHORN AND P. A. S. CANHAM (*Amer. J. Path.*, March-April, 1959) have produced histochemical and quantitative chemical data which reveal that the uptake of iron from iron-enriched diets is much greater in rats fed a "bad" (maize-meal) diet than those fed a "good" (stock) diet. This increased iron uptake by rats consuming iron-enriched mealie-meal is reflected in the far greater total carcass iron despite the smaller daily and total iron ingested. It is also characterized by lesser growth of these rats when compared with other groups. Dietary siderosis in rats is characterized by an accumulation of histochemically demonstrable iron in liver cells before it appears in hepatic phagocytes or other parenchymal cells. Iron absorbed in excess seems to accumulate in the liver to a large extent before other non-reticulo-endothelial organs become notably siderotic. In these respects the lesions in rats resemble those in the early stages of African dietary siderosis. The colon becomes heavily laden with iron, whereas the duodenum remains virtually free of it even in heavily siderotic rats. The histochemically and chemically determined distribution of iron in these experiments, taken in the light of data from the literature, adds additional information in support of the possibility that the underlying lesion in nutritional siderosis pertains to the intracellular iron-containing enzymes located on the mitochondria. The role of intracellular hypoxia (or anoxia), perhaps induced by malnutrition, in increasing the speed and degree of iron uptake and the onset of hepatocellular siderosis, is discussed in the light of the present results. It is concluded that dietary siderosis in rats and, perhaps, in man, too, is not due to iron overload alone, but may rather be attributable to some effect of a "bad" diet on intracellular metabolism.

Whipple's Disease.

J. C. SIERACKI AND G. FINE (*A.M.A. Arch. Path.*, January, 1959) present five cases of Whipple's disease which show a more generalized involvement than has been described in most previous reports. The morphological basis for defining the systemic involvement is a characteristic cytoplasmic particle found most commonly in histocytes. The organs involved in addition to the gastro-intestinal tract have been the heart, lungs, spleen, pancreas, mesentery and retroperitoneal tissues, adrenal glands, brain and various structures of mesodermal origin.

Renal Function in Burned Patients.

I. G. GRABER AND S. SEVITT (*J. clin. Path.*, January, 1959) studied the renal function in 17 extensively burned patients admitted and treated by intravenous therapy within one to three and a half hours after burning, and the findings

have been correlated with the renal histological changes in those who subsequently died. Patterns of glomerular and tubular function were established, which conflict with the concept that acute renal failure is characterized by loss of tubular function, that it is due to renal tubular necrosis, and that severe oliguria or anuria is always present. The major dysfunction according to the findings of these authors is glomerular and not tubular, even though tubular necrosis and blockage by casts are often found. The ætiological factors relating to glomerular and tubular function are discussed and attention is drawn to a possible structural change in the glomeruli which could account for the persistent fall in the glomerular filtration rate.

Spleen and Lymph Node Changes in Cirrhosis.

S. GLAGOV, G. KENT AND H. POPPER (*A.M.A. Arch. Path.*, January, 1959) have been able to demonstrate that there is an increase in pyroninophilia in cells both of the plasma cell and of the lymphoid series in the splenic red pulp and medullary cords of lymph nodes in cirrhosis of the liver. There was no significant increase in the splenic white pulp or in the lymphoid follicles. The distinctive pattern of the pyroninophilia and its correlation with serum gamma-globulin levels suggest that the spleen and lymph nodes represent sites of gamma-globulin production in cirrhosis.

THERAPEUTICS.

Kanamycin, a New Antibiotic.

G. ANDRIEU *et alii* (*Presse méd.*, April 11, 1959) have carried out an experimental study *in vitro* of kanamycin, a new antibiotic, and present the following conclusions. Its action is essentially bactericidal, and only low concentrations are required. It is effective against a number of microorganisms, especially staphylococci and *Proteus*. It is little affected by pH, and seems to be independent of the presence of serum. Strains of bacteria repeatedly subjected to the action of kanamycin develop a progressive resistance, but slowly and in general to only a moderate degree. This resistance to kanamycin developed *in vitro* does not bring about any reduction in sensitivity to penicillin, the tetracyclines, chloramphenicol, erythromycin, oleandomycin, spiramycin, carbomycin, bacitracin or novobiocin. It appears that, at least for certain strains, a combination of penicillin and kanamycin may have a synergistic effect on the bactericidal action *in vitro*. Acquired resistance to kanamycin seems to be accompanied by cross-resistance to neomycin and framycetin, and vice versa. On the other hand, while strains that have become resistant to kanamycin present cross-resistance to streptomycin, strains that have become highly resistant to streptomycin retain their sensitivity to kanamycin practically unchanged. A comparative study of sensitivities to kanamycin and to the other antibiotics at present in use shows that it is active against a large number of strains resistant to one or more of the other antibiotics. Moreover, statistical analysis of the results obtained with a homogeneous group of staphylococci reveals no correlation between their sensitivities to kanamycin and to any one of the other antibiotics. The authors state that their other experimental findings are equally encouraging. The antibiotic is rapidly absorbed by the intramuscular route; estimations of blood level show that a high concentration is achieved in the first quarter of an hour, the figure falling progressively over some hours. It is well absorbed, except in the muscles and the brain. Urinary excretion is good, in concentration even higher than that of streptomycin. Animal studies showed that the administration of kanamycin was associated frequently with renal lesions, which were reversible; the toxic effect on nerves seemed slighter than that of streptomycin. The first clinical trials of kanamycin suggest that it will have a place in the antibacterial armamentarium, and that it will be of use in the treatment of certain serious infections, especially those due to the staphylococcus and to certain intestinal bacteria.

Staphylococcal Endocarditis Treated with Ristocetin ("Spontin").

R. W. WEBER (*J. Amer. med. Ass.*, November 8, 1958) records two patients with endocarditis due to *Staphylococcus aureus* who were treated successfully with ristocetin. Each patient was critically ill and the exhibition of ristocetin was associated with prompt clinical improvement and eventual bacteriological cure. One patient, aged 32 years, had chills and fever up to 104° and 105° F. in spite of treatment with penicillin, streptomycin, oxytetracycline, chlortetracycline and novobiocin. The heart was enlarged and a grade 2 systolic murmur was heard in the left third interspace. Blood cultures revealed the presence of hæmolytic *S. aureus*, which was moderately sensitive to erythromycin, chloramphenicol and nitrofurantoin. Erythromycin was then given in doses of two grammes every six hours for 14 days. The results of blood cultures were then negative, but severe nausea and vomiting developed, and the dose of erythromycin was reduced to one gramme every six hours. The patient being still critically ill, ristocetin was given intravenously, 1·5 grammes in 500 ml. of 5% glucose solution every eight hours. The temperature became normal as soon as treatment with ristocetin was instituted and remained so. The dose of ristocetin was gradually reduced, a total of 44 grammes being given. Serum concentrations of 40 to 80 μg. per ml. of ristocetin were maintained during treatment. The patient made a complete recovery. The second patient followed a similar course. In each patient severe leukopenia and neutropenia occurred, but the white cell count gradually returned to normal.

Chlorothiazide and the Blood Uric Acid Level.

B. G. OSEN, M. RICH AND M. S. BELLE (*J. Amer. med. Ass.*, December 20, 1958) record the effect of treatment with chlorothiazide in raising the blood uric acid level. Patients who were given 0·5 gramme of chlorothiazide twice daily so that the dose of reserpine could be reduced in the treatment of hypertension were found to have a raised blood uric acid level from 6·5 to 11·5 mg. per 100 ml. Pains in the feet and even swelling and tenderness of the great toes were noted in some patients. It is suggested that the use of chlorothiazide may have in this way induced pains in the feet. It was found that when chlorothiazide was suspended the pains in the feet ceased. However, of 12 patients studied only three had pains in the feet. It is suggested that the raised uric acid level may be due to loss of fluid from the body or that there may be an effect on the kidneys causing them to retain uric acid.

The Use of Chlorothiazide in the Nephrotic Syndrome.

J. E. BURCH AND H. A. WHITE (*A.M.A. Arch. intern. Med.*, March, 1959) discuss the use of chlorothiazide in the nephrotic syndrome. Detailed case histories of 10 patients with the nephrotic syndrome associated with various types of renal disease are presented. An initial dose of 0·5 gramme of chlorothiazide was given orally to these patients twice daily, and in all cases an effective diuresis followed. In most cases other diuretic measures had failed, and chlorothiazide proved to be non-toxic but therapeutically effective. Among the clinical advantages of chlorothiazide are: (i) remarkable effectiveness when administered orally; (ii) prompt diuretic action, consisting of water diuresis, natruresis and chloruresis but only minimal kaluresis; (iii) persistent activity and lack of tolerance until œdema subsides; (iv) anti-hypertensive action; and (v) minimal side-effects or toxic reactions. The diuretic response appears to be due to decreased tubular reabsorption of water, sodium and chloride. When properly integrated with other well-established clinical procedures this drug should prove to be therapeutically beneficial in some patients with the nephrotic syndrome and should at least be given a therapeutic trial. Whether or not it has any "curative" value on the renal lesion remains to be determined, but it may prove valuable indirectly by reducing arterial blood pressure and eliminating the water-logged environment of vital cells of the body, including those of the nephron.

Glucocorticoids in The Treatment of Typhoid Fever.

C.-F. COLUCCI (*Presse méd.*, April 11, 1959) has studied the effect of synthetic glucocorticoids given alone or in association with chloramphenicol in the treatment of typhoid fever. He compared the results obtained with those from a control series of patients treated with chloramphenicol alone. The author states that the hormones were well tolerated, even when they were given for long periods; however, as the sole therapeutic agent they produced in most cases only a slight effect, although in a few they brought about a prompt and complete recovery. On the other hand, treatment with chloramphenicol and prednisone in combination was very effective, and much superior to treatment with one or other agent alone. The author discusses the technique of the combined treatment in detail; the method used is one which he has developed.

Special Correspondence.

PARIS LETTER.

From our Special Correspondent.

New Treatment of Leukæmia.

THE public Press in France has recently been much occupied with attempts at treating leukæmic children by massive total radiotherapy followed by the reinjection of bone marrow taken from donors.

At the end of last year some Yugoslav atomic scientists, dangerously irradiated as the result of an accident at an atomic pile, were sent urgently to France to receive the appropriate treatment. One of these scientists died from completely irreversible lesions of the digestive tract. The others, whose marrow and blood were progressively denuded of erythrocytes and leucocytes as a result of the irradiation, were able to survive, thanks to bone-marrow grafts. These bone-marrow grafts presented delicate problems of immunohæmatology, and it was particularly difficult to discover whether the new cells reformed in the blood of the accident victims were cells from the donors, or blood cells which had escaped the irradiation and which had reproduced themselves under cover of intercurrent transfusions. As a result of the success obtained in the treatment of these atomic scientists from Yugoslavia, the Press thought that it was a good idea to publicize the therapeutic trials actually carried out on leukæmic children in the clinic of Professor Jean Bernard. Several bone-marrow grafts have been carried out, but leukæmia is a capricious disease. No one can predict its duration, and leukæmic subjects treated by very ordinary methods have been known to live for several years. Thus, before one can state that the treatments undertaken today in a few cases have been effective, it is necessary to wait for a lapse of time corresponding to the normal evolution of a case of leukæmia. It is therefore impossible to state definitely that cures have been effected by this method of treatment, even in comparison with the cases of these Yugoslav scientists, since their blood was normal before the accidental irradiation. In the case of leukæmic subjects, on the other hand, the irradiated blood was diseased blood, and it is therefore impossible to state whether the blood which reforms after the graft will be normal blood or diseased blood.

Original Clinical Work, January-February, 1959.

Amongst the original clinical works of particular interest in the first two months of 1959, the following are noted.

Work has been done on the physiopathology of hæmorrhagic accidents associated with hæmorrhoids.[1] Anatomical considerations and classical physiopathological concepts do not satisfactorily explain hæmorrhagic accidents associated with hæmorrhoids. Actually venous dilatations are often discrete, and the histological signs of chronic inflammation may be absent in the course of such accidents. This clinical study stresses the existence of "red proctitis" (mucous membrane rich in pigmented and dilated capillaries masking poorly-developed groups of veins). Histological examination reveals a submucous vascular network rich in pre-capillary segments, with muscle coats capable of playing a part in the regulation of the local circulation. Again, histological examination and also injection into the vascular system of contrast media reveal the circulatory autonomy of this submucous and pre-capillary network independent of the system of hæmorrhoidal lakes. By means of arterio-venous shunts, the bright oxygenated blood can flow into the veins by short-circuiting the capillaries; from this result those occasionally massive hæmorrhages of red blood, the mechanism of which recalls that of certain hæmorrhagic forms of gastritis.

Thus hæmorrhoidal hæmorrhage without hæmorrhoids may be explained; the functional vascular disorder triumphs over varicose hypertrophy.

Another interesting piece of research has been an attempt to discover whether the pathogenic effect of gluten in cœliac disease results from an enzyme deficiency or from an allergic reaction. Professor Breton[2] has tried to answer this question. The results of the radiological tests carried out by this worker have made it possible to verify the pathogenic action of gliadine as well as of its various enzymatic hydrolysates. The protective effect afforded by the addition of an extract of the intestinal mucosa of the pig strongly suggests an anomaly in intestinal absorption, probably of enzymatic type. Actually the results of cutaneous tests for allergy have not made it possible to demonstrate on the skin sensitization to gliadine or to any of its enzymatic hydrolysates. The specific harmful effect of gliadine must therefore be sought in its chemical composition and in a very special disturbance of its breakdown. This worker points out that it is the special chemical character of this substance and the specific action of the intestinal digestive enzymes which are responsible for the liberation of a toxic peptide. From the therapeutic point of view, he hopes that the addition of special digestive enzymes may improve the prognosis of a disorder whose progress the most strict attention to diet is not always able to check, and which is still too often grave.

Still in the sphere of clinical and physiopathological research, we find, in an interesting article on the metabolism of electrolytes studied by radioactive isotopes, the description of an ingenious analogical method which makes it possible to overcome easily the difficulties in interpreting the results obtained by these methods.[1] The analogical machine in question is a sort of billiard table, on which red balls and black balls are set out initially in a particular way. The latter are then shaken about by a Brownian movement. By the use of this machine, it is possible to reproduce mechanically biological experiments of the most complex type, and to study by analogy all the experiments with radioactive isotopes that can be imagined in physiology. Without mathematical interpretation, it is possible, after a few minutes of agitating the billiard table, to see whether the theoretically calculated results agrees with the experiment. It seems that this simple method should be brought to the knowledge of all researchers who have not adequate mathematical training to study biological phenomena with radioactive isotopes.

Finally, to end this study of interesting publications in the clinical and physiopathological field, attention is drawn to some work on the epileptico-endocrine syndrome of diencephalic origin.[2] The authors describe the association of a type of epilepsy of deep centrencephalic origin and of endocrine disorders of diencephalic origin, this duality of clinical findings being explained by a single common intracerebral traumatic factor. With disorders of thirst, sleep, hunger and obesity are associated epileptic manifestations of centrencephalic type (isolated myoclonia or myoclonia alternating with generalized crises, isolated loss of consciousness, or loss of consciousness alternating with myoclonia and crises, or even vegetative crises). The electroencephalogram reveals the centrencephalic origin of these crises, which anatomical verification sometimes makes it possible to confirm by revealing localized lesions at the base of the brain, the lateral border of the third ventricle, the hypothalamus or the region of the aqueduct of Sylvius. The evolution of this diencephalic epileptico-endocrine syndrome depends essentially on the ætiology of the hypothalamic lesions. It has been possible to remove some tumours surgically, and the operative intervention has been followed by complete regression of the clinical disorders. Drainage of the third ventricle also ultimately produced disappearance of the disorders. It has also been possible to remove surgically certain inflammatory adhesions, the abolition of which has produced a decided improvement. However, the exact ætiology is difficult to determine and often the indications for operation are hard to set down exactly.

The Heart-Lung Machine with Artificial Pulmonary Membrane of J. André Thomas.

A small number of artificial heart-lung machines is at present in use in the world. In a very recent number of the *Semaine des Hopitaux*, J. Vaysse and his colleagues[3] present an accurate description of the French apparatus of André Thomas, which they have been using for more than a year. It is a heart-lung machine with artificial pulmonary membrane. In this apparatus, hæmatosis takes place across a membrane, and the underlying technical design permits easy oxygen saturation of more than six litres of blood per minute with minimal hæmolysis. The apparatus therefore makes it possible to operate on an open heart in adults with an average flow varying between 1·7 and 6·4 litres per minute, during periods varying from 12 to 50 minutes. The authors describe the 35 operative

[1] Soullard, J., Richir, Cl., and Madesclaire, G., 1959, *Presse méd.*, 67 : 179.

[2] Breton, A., Vandendorp, F., and Dubois, O., 1959, *Pédiatrie*, 14 : 5.

[1] Bernier, J.-J., and Nagnien, P., 1959, *Concours méd.*, 81 : 331.

[2] Boudin, G., and Barbieet, J., 1959, *Concours méd.*, 81 : 227.

[3] Vaysse, J., *et alii*, 1959, *La Semaine des Hôpitaux*, 35 : 722.

interventions which they have carried out, and conclude that in this type of surgery on the open heart, the prognosis depends very little on the extracorporeal circulation itself, but primarily on the pathological condition of the heart on which the operation is being performed, and on the heart's tolerance to the repairs that have been carried out.

New Therapeutic Ideas.

Amongst the therapeutic ideas which we find particularly interesting, and which have been recently published in the French Press, we may draw attention to the following articles.

Treatment of Advanced Cancer of the Breast by Adreno-Splenic Transplantation.

In the case of a woman who has not undergone any hormone treatment, whether treatment is a question of ovariectomy or of hormone therapy, Professor Dargent[1] begins by suggesting ovariectomy followed by a course of treatment with testosterone. There is an increasing tendency to refuse to prescribe male hormones for a woman who has not been previously sterilized. So long as this form of treatment is successful, one must defer operation on the adrenal glands. If hormone therapy thus carried out is also a dead loss, one must also refuse operation on the adrenal glands; but when hormone therapy has given satisfactory results for some time and metastases again appear, one may then suggest a new operative approach.

The author has chosen adreno-splenic transplantation. When there is no local or general contraindication, the author carries out in the first stage an adrenal transplantation to the interior of the spleen, the vasculo-nervous pedicle of the gland being preserved. A fortnight later, right adrenalectomy is performed. As a result of this technique, which drains the adrenal blood directly towards the liver by the splenic vein, one obtains results as good as those achieved by bilateral adrenalectomy, for the sex hormones are broken up in the liver, and yet complete cessation of cortisone therapy is possible, for there remains in circulation enough of this hormone to make permanent cortisone therapy unnecessary.

The author has carried out this operation in 24 cases. In seven the objective results have been very good. The most spectacular results were obtained in bony, pleuro-pulmonary and ocular metastases, and in lesions of the soft tissues.

There is no particular type of cancer in which this transplantation is specially indicated. The great advantage of the procedure is the fact that it abolishes the need for post-operative cortisone therapy.

On the question of adrenal surgery, the author holds that one must choose transplantation whenever it is technically possible, or bilateral adrenalectomy when there are adrenal metastases. This indication for bilateral adrenalectomy is one of the most conclusive.

New Forms of Chemotherapy for Mental Illnesses.

The team of workers headed by Professor J. Delay,[2] at the Psychiatric Hospital of Saint Anne, are carrying out exhaustive tests of a new neuroleptic which seems likely to have a bright future. The drug 78 43 R.P. (manufactured by Specia and not yet on the market), is a sulphonamide derivative of phenothiazine. It is a major tranquillizer of powerful and complex action, which produces remarkable improvements in chronic or resistant schizophrenia and even in mental deficiency. The treatment requires interrupted administration of the drug and careful observation in hospital. It must be used only to treat persons in good general health. The beneficial effects of the drug are observed at the completion of treatment or in the intervals of treatment. However, a warning is given that there may be disturbances of the psyche in the form of euphoria in case of overdosage, but there are no harmful sequelæ. The initial dose is 10 mg. per day, increased progressively up to an average dose of 50 mg. per day.

On the same subject of chemotherapy of mental diseases, it should be mentioned that Professor Jean Delay and his co-workers[3] have also published an article on the treatment of depressive states by isonicotinic derivatives and particularly iproniazid, which is not a tranquillizer but an anti-depressive. By its action on the function of sleep, iproniazid resembles the psychotonic amines. It acts particularly on depressive and asthenic states, in which, as is well known, the progress of chemotherapy has been relatively slow. The maximal dose of iproniazid employed is 0·15 gramme per day.

In the same issue of the *Annales médico-psychologiques*, M. Fouks and his co-workers record the results of their therapeutic trials with a new neuroleptic, 55·01. (This drug is not yet on the market; it is manufactured by Delalande Laboratories.) The drug is a combination of phenothiazine and piperazine. It has a powerful neuroleptic action resembling that of "Largactil". Its action on psychomotor excitement is often remarkable, particularly in cases of acute agitation. It appears that this drug may be less toxic than the other neuroleptics. It has no secondary effects, even in high dosage (the author advises a daily dose of 0·5 to 1·0 gramme).

The Premenstrual Syndrome.

To conclude, let us draw attention to an interesting article on the treatment of the premenstrual syndrome, in which Dr. J. Durlach,[1] after studying different forms of treatment that have been recommended up to the present time, suggests the employment of potassium nitrate in gluten-covered dragées in doses of 0·25 gramme. Potassium nitrate has an acidifying, chloride-removing, sodium-removing and therapeutic action, and therefore it seems to the author the treatment of choice for the hydro-electrolytic disorder of the premenstrual syndrome. He has used this drug in 42 cases, and in 37 achieved good or excellent results. The initial effective dose was most frequently 2·25 grammes per day, and the maintenance dose 1·50 grammes. The treatment must be begun on the day before the usual date of appearance of the syndrome and continued until menstruation commences. If the results are excellent with the initial dose, in succeeding months the maintenance dose is used. In case of poor results, the author adds meprobamate to act on the other pole of the physiopathological "vicious circle" of the premenstrual syndrome.

[1] Dargent, M., and Mayer, M. (1959), *Mém. Acad. Chir. (Paris)*, 85: 112-122.

[2] Delay, J., *et alii*, 1959, *Press méd.*, 67: 123.

[3] Delay, J., *et alii*, 1959, *Ann. méd.-psychol.*, 117: 125.

[1] Durlach, J., 1959, *Concours, méd.*, 81: 319, 411.

Correspondence.

MEDICINE AND ATOMIC ENERGY.

SIR: In support of Dr. Benwell (MED. J. AUST., June 20) I would suggest that our chances of a genocidal war are about even. With the poor present prognosis, it would seem realistic to practise at least as much prophylaxis as therapy. A few tons of timely medico-political propaganda may be worth a megaton of makeshift "cure".

War has been prevented. It depends solely on civil law replacing martial law. This has been proved: in Europe, as knights errant and feudal fortresses and their alliances gave painful birth to parliaments and police; in the Swiss valleys, where Catholic and Protestant, French and German cantons mutilated each other until they saw outside greater threats, and federated into one of the world's most peaceful nations; in North America, where gun duels settled disputes with "law men" and their posses until judge and jury were entrenched; and in every peaceful community, from the tribal horde to the mightiest federations.

People will not have the United Nations take over their migration quotas, tariff pressures, currency exchange, rail gauges, traffic rules, schools or water supplies; but they are ready to have the United Nations take over all their defence forces. Over half of labour and of non-labour voters agreed to this, according to Australian public opinion polls. Other countries report similar majorities.

The World Association of World Federalists, growing powerful in America, Europe and Japan especially, is backed by hundreds of members of the Association of Parliamentarians for World Government. These movements work to inform our leaders of this popular approval of world law, and to convince people of the need to hustle their governments towards a world authority with limited but adequate powers to make laws over arms, and to police and judge those laws, which shall bind every individual.

There is a 500 page published blueprint for the necessary changes in the United Nations Charter and broadening of United Nations representation: "World Peace through World Law" (1958) by Clark and Sohn, two leading

American International Law authorities. The Charter is set down for early review by a United Nations Committee.

There are plain statements by the Premiers of the United Kingdom, United States, France, India and other nations in support of this need, but no such statement yet from an Australian or Russian politician. There are clear recommendations of the federalist reform from nuclear scientists; the late Pope Pius XII; the Methodists and Quakers of America; Lord Boyd Orr of our own profession, a Nobel Prize winner and first director of the Food and Agriculture Organization; Dr. Brock Chisholm, first president of the World Health Organization; and the Australasian Peace Assembly, which until recently seemed to favour only the communist approach to peace. But there are, so far, no words from the World or the British Medical Associations or their officials, I believe. We dig ditches for plasma stockpiles in guilty silence, except for a rather oblique approval of world law by your editorial "War, Peace and the Doctor" (May 3, 1958).

Yours, etc.

Post Office Box 328, Rockhampton, Queensland.
June 24, 1959.

DOUGLAS EVERINGHAM.

MEDICO-LEGAL ASSOCIATION OF NEW SOUTH WALES.

SIR: It has been suggested that an attempt should be made to revive the Medico-Legal Association of New South Wales. Several members of our profession have expressed a wish that this should be done, and I understand that the legal profession is also interested.

I would be grateful if those who share this view would communicate with me as soon as possible. If the response is adequate, a meeting will be called to elect office bearers and decide on a policy for the conduct of the Association. I presume it is not necessary to emphasize the benefits which could arise from membership of such an organization. It would permit an exchange of views on a wide variety of subjects of mutual interest, and also serve to iron out any difficulties which might have arisen in the past between two professions which have not had any common meeting ground.

Yours, etc.

183 Macquarie Street, Sydney.
June 27, 1959.

J. MCGEORGE.

CANCER, A DISEASE OF THE NERVOUS SYSTEM.

SIR: I do not profess to know much about cancer, and, I fear, have only an occasional interest in the topic, but Dr. Llewellin Davey's letter (May 30, 1959) suggesting that the process may be due to loss of trophic nervous control, awakens a memory.

In THE MEDICAL JOURNAL OF AUSTRALIA, March 1, 1930, there was an article by the late Professor D. A. Welsh, in which he says: "Neoplasia may be the expression or fulfilment of a need of the parent organism . . ." and "its object may be compensatory or defensive, though perverted and disastrous in its results".

This article was followed in the same year, under the authorship of A. Wolseley D'Ombrain, E. H. Burgmann and R. S. Lee, by a lengthy and erudite contribution to the correspondence column of *The Journal of the Cancer Research Committee* entitled "The Function of Cancer". This letter dealt with the development of cancer from a psychogenic aspect, and gave a tentative psychoanalytic explanation. It was so modern and original in thought that I sent a copy to the late Dr. Ernest Jones, of psychoanalytic fame, in London. He expressed the opinion that it was of very great interest and contained the possibility of truth, but that no work had yet been authoritatively carried out upon the subject.

It would seem that the repeated application or ingestion of irritants—the latter including devitalized and preserved foods—might have some bearing on the health of the particular cell structure involved. The food idea is a fairly old one, but is probably just as rational as the many other somewhat fanciful theories suggested. The site of pathological change may possibly be selected by psychological disturbance.

It is apparent that no one factor alone produces cancer, and its genesis comprises as yet unknown elements in the human metabolism, so that, as Dr. Davey truly remarks, "chronic irritation long-continued, whether mechanical, chemical or bacterial, seems to be the only cause of cancer yet agreed to". Since with our increasing knowledge of psychosomatic influences many diseases have been reasonably explained, the aetiology of which had been a mystery, and since we know that continued emotional distress may produce tissue changes, may not a great part of this chronic irritation be discovered eventually, to be psychogenic?

Yours, etc.

235 Macquarie Street, Sydney.
June 26, 1959.

E. HASLETT FRAZER.

THE AUSTRALIAN COLLEGE OF GENERAL PRACTITIONERS.

SIR: The report of the annual meeting in your issue of June 20, 1959, will no doubt draw the attention of general practitioners to our College. At present there are nearly a thousand members of the College in Australia, but there may be others who are eligible and who would like to become members. Inquiries re the College can be made to the following honorary secretaries of the State Faculties:

Dr. A. Rumore, Honorary Secretary, New South Wales Faculty, 203 Macquarie Street, Sydney, N.S.W. R. Spence, Esq., Secretary, Queensland Faculty, Box 1498V, G.P.O., Brisbane, Q. Dr. R. Greenlees, Honorary Secretary, South Australia Faculty, 80 Brougham Place, North Adelaide, S.A. Dr. Peter Fay, Honorary Secretary, Tasmania Faculty, 174 Macquarie Street, Hobart, Tas. Dr. D. Zacharin, Honorary Secretary, Victoria Faculty, 132 Grey Street, East Melbourne, Vic. Dr. J. Watson, Honorary Secretary, Western Australia Faculty, 8 King's Park Road, West Perth, W.A.

Yours, etc.

W. A. CONOLLY, President.
The Australian College of General Practitioners, 203 Macquarie Street, Sydney.
June 23, 1959.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

MENTAL DISEASE IN NEW SOUTH WALES.[1]

[From the *Australasian Medical Gazette*, November, 1896.]

THE report for 1895 of the Inspector-General of the Insane for New South Wales has been presented to Parliament. In it we learn that on 31st December 1895 there were 3,720 insane persons under official cognisance. The number at the close of 1894 was 3,587, so that the increase during the year amounted to 133, which is above the average for the last 20 years, though somewhat below that for the year 1894. Dr. Norton Manning states that the causes which led to the unusual increase during 1892-3 and 4, and which were pointed out in the report for the latter year, appear to have been still in operation in 1895. The proportion of insane to population from 1872 to 1891 was nearly stationary at 2·69 per thousand, whereas during the last four years it has slowly risen, and now stands at 2·91 per thousand. The chief moral causes of insanity during 1895, as far as can be ascertained with accuracy, were: 1. mental anxiety and worry and overwork: 2. domestic trouble: 3. adverse circumstances, including pecuniary difficulties. The chief physical cause was intemperance in drink. The chief cause of death was general paralysis. The cost to the State for each patient in the hospitals for the insane during 1895 was £24.6.4, or 954d. per week. The report is a most satisfactory one, and reflects credit on the Inspector-General and all his officers.

[1] From the original in the Mitchell Library, Sydney.

British Medical Association.

SIR CHARLES HASTINGS AND CHARLES OLIVER HAWTHORNE CLINICAL PRIZES, 1960.

THE Sir Charles Hastings Clinical Prize Competition was established by the British Medical Association for the promotion of systematic observation, research and record in general practice. The competition has been extended by the addition of a second prize known as the Charles Oliver Hawthorne Clinical Prize. The following are the regulations governing the awards:

1. The Sir Charles Hastings Clinical Prize, consisting of a certificate and £75, will be awarded for the best entry.

2. The Charles Oliver Hawthorne Clinical Prize, consisting of a certificate and £50, will be awarded for the second-best entry.

3. Any member of the Association who is engaged in general practice is eligible to compete for these prizes.

4. The work submitted must include personal observations and experiences collected by the candidate in general practice, and a high order of excellence will be required. If no work entered is of sufficient merit, no award will be made. Candidates in their entries should confine their attention to their own observations in practice rather than to comments on previously published work on the subject, though reference to current literature should not be omitted when it bears directly on their results, their interpretations and their conclusions.

5. Entries must be sent to the Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1, not later than December 31, 1959.

6. A prizewinner in any year is eligible for an award of either of the prizes in any subsequent year. A study or essay that has been published in the medical Press or elsewhere will not be considered eligible for a prize, and a contribution offered in one year cannot be accepted in any subsequent year unless it includes evidence of further work.

7. If any question arises in reference to the eligibility of the candidate or the admissibility of his or her entry, the decision of the Council on any such point shall be final.

8. Preliminary notice of entry for this competition is required, on a form of application to be obtained from the Secretary.

9. Each entry, which should be unsigned, must be typewritten or printed on one side of the paper only, and accompanied by a separate note of the candidate's name and address.

10. No definite limits are laid down as to the length of the work submitted, but the Council anticipates that for this competition 3000 to 10,000 words would be suitable.

11. Inquiries relative to the prizes should be addressed to the Secretary.

PRIZE ESSAY COMPETITION FOR PROVISIONALLY REGISTERED PRACTITIONERS, 1960.

THE Council of the British Medical Association is prepared to consider the award, in 1960, of prizes to provisionally registered practitioners for essays submitted in open competition.

The subject of the essay is "What Defects do you now Recognise in your Medical Education, and how do you Think they Might be Remedied in the Future?"

Any provisionally registered practitioner in the pre-registration year at the time of submission of the essay is eligible to compete for a prize. No study or essay that has previously appeared in the medical Press or elsewhere will be considered eligible for a prize.

If any question arises in reference to the eligibility of a candidate or the admissibility of his or her essay, the decision of the Council of the British Medical Association shall be final. Should the Council decide that no essay entered is of sufficient merit, no award will be made.

At least one prize of £50 is offered. In determining the number of prizes to be awarded, the Council will take into consideration the number and standard of essays received.

Essays must not exceed 5000 words, and must be typewritten or legibly written in the English language on foolscap paper, on one side only, must be unsigned, and must be accompanied by a note of the name and address of the entrant. Notice of entry for this competition is necessary, and a form of application can be obtained from the Secretary of the British Medical Association.

Essays must be forwarded so as to reach the Secretary of the British Medical Association not later than December 31, 1959.

Inquiries relative to the competition should be addressed to the Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

PRIZE ESSAY COMPETITION FOR MEDICAL STUDENTS, 1960.

THE Council of the British Medical Association is prepared to consider the award, in 1960, of prizes to medical students for essays submitted in open competition.

The subject of the essay is "Why I Chose Medicine and What I Hope to Achieve".

Prizes of £25 will normally be offered, but the Council will take into consideration the number and standard of the essays received when determining the awards to be made.

Any medical student who is a registered member of a medical school in the United Kingdom, Commonwealth and Empire or the Republic of Ireland at the time of submission of the essay is eligible to compete for a prize.

Previous prizewinners are eligible for a second award.

If any question arises in reference to the eligibility of a candidate or the admissibility of his or her essay, the decision of the Council of the British Medical Association shall be final. Should the Council decide that no essay entered is of sufficient merit, no award will be made.

Essays must not exceed 5000 words, and must be typewritten or legibly written in the English language on foolscap paper, on one side only, must be unsigned, and must be accompanied by a note of the name and the medical school of the entrant. Notice of entry for this competition is necessary, and a form of application can be obtained from the Secretary of the British Medical Association.

Essays must be forwarded so as to reach the Secretary of the British Medical Association not later than December 31, 1959.

Inquiries relative to the competition should be addressed to the Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

Medical Matters in Parliament.

HOUSE OF REPRESENTATIVES.

THE following extracts from *Hansard* relate to the proceedings of the House of Representatives on April 23, 1959.

Hospital Benefits Scheme.

MR. BRYANT: I ask the Minister for Health a question without notice. Yesterday, in reply to a question on notice about hospital benefits for aged persons and the difficulties experienced by some institutions in getting the guaranteed fund benefits, the Minister said:

> The principle of selecting the patients and not the hospital for the purposes of the guaranteed fund benefits was thoroughly investigated and found to be administratively impracticable.

Can the Minister explain in what way it is administratively impossible to give these fund benefits to the people who are patients in the smaller hospitals, which are principally concerned in this matter?

DR. DONALD CAMERON: Prior to the introduction of amendments to the National Health Act last year, there was always a considerable number of hospitals in which fund benefit was not paid. I made it clear in the House that when the special accounts procedure was introduced there would still be a number of institutions in which special accounts benefit, which is in this case fund benefit, would not be paid. Those institutions, as I explained at

the time, have always been in receipt of Commonwealth benefit, and still continue to receive it. I want to point out also to the honorable gentleman that the purpose of the amendments to the act was not to provide assistance to hospitals but to individuals.

Influenza.

MR. STEWART: My question without notice is addressed to the Minister for Health. Is it a fact that thousands of persons who have been inoculated with a serum produced by the Commonwealth Serum Laboratories as a safeguard against influenza are living in a fool's paradise, firmly believing that they are immune to the present epidemic raging throughout Australia, when the true position is that the serum has been found to be ineffective as a protection against variants of the influenza germ?

DR. DONALD CAMERON: No, I do not think that is a fact at all. The Commonwealth Serum Laboratories produce, not a serum, but a vaccine, against influenza. It has a very considerable degree of potency, but not, I think, 100 per cent effectiveness, against influenza. The honorable gentleman must realize that the word "influenza" is frequently used as a not very precise term, and that whilst a person may receive an inoculation of an anti-influenza vaccine which, in fact, prevents him from developing influenza in the strict sense of the term, he may still develop other respiratory diseases closely similar in their clinical manifestations to influenza.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Week-end Course in Psychosomatic Medicine.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that a week-end course in psychosomatic medicine for general practitioners will be held in the Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital, under the chairmanship and supervision of Professor W. H. Trethowan, on Saturday and Sunday, August 8 and 9, 1959. The programme will be as follows:

Saturday, August 8: 2.15 p.m., "Psychosomatic Problems in General Practice", Dr. T. M. Greenaway; 3 p.m.: "Premenstrual Tension Syndrome", Dr. Ralph Reader and Dr. D. C. Maddison; 4.15 p.m., "Psychosomatic Problems in Gynæcology", Dr. Malcolm Coppleson.

Sunday, August 9: 10 a.m., "Psychosomatic Aspects of Surgical Practice", Dr. D. C. Maddison; 11 a.m., "Mental Manifestations of Metabolic Disorders", Dr. John Ellard; 11.45 a.m., "Physical Aspects of Emotional Disturbance in Childhood", Dr. F. W. A. Clements; 2.15 p.m., "Rheumatoid Arthritis and Non-Articular Rheumatism", Professor W. H. Trethowan and Dr. John Sands; 3.45 p.m., panel discussion, "Any Questions?", Dr. T. M. Greenaway, Dr. Ralph Reader, Dr. Malcolm Coppleson, Dr. John Ellard, Dr. F. W. A. Clements, Dr. John Sands.

The fee for attendance is £3 3s., and those wishing to attend are requested to notify the Course Secretary, The Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney. Telephone BU 4497-8.

Naval, Military and Air Force.

APPOINTMENTS.

THE following appointments, changes, etc., are published in the *Commonwealth of Australia Gazette*, No. 31, of May 21, 1959.

NAVAL FORCES OF THE COMMONWEALTH.

Permanent Naval Forces of the Commonwealth (Sea-Going Forces).

Appointments.—Kenneth Nicholson Howson is appointed Surgeon Lieutenant (for Short Service) (on probation), dated 23rd March, 1959.

Confirmation in Rank.—Surgeon Lieutenant (on probation) Terence Joseph Horgan is confirmed in the rank of Surgeon Lieutenant (for Short Service), with seniority in rank of 11th January, 1958, dated 11th January, 1959.

Promotions.—Sub-Lieutenant (U.) (on probation) Cyril Francis Elliott is promoted to the rank of Surgeon Lieutenant (on probation), dated 1st March, 1959. Surgeon Lieutenant (D.) (for Short Service) Jonathan Hartland Herbert is promoted to the rank of Surgeon Lieutenant-Commander (D.) (for Short Service), dated 7th March, 1959.

Confirmation in Rank.—Surgeon Lieutenant (for Short Service) (on probation) Hugh Peter Harney Ivens is confirmed in the rank of Surgeon Lieutenant (for Short Service), with seniority in rank of 12th March, 1958, dated 12th March, 1959.

Citizen Naval Forces of the Commonwealth.

Royal Australian Naval Reserve.

Promotions.—Surgeon Lieutenant John Hunter Stephenson is promoted to the rank of Surgeon Lieutenant-Commander, dated 2nd March, 1959.

Termination of Appointment.—The appointment of John Lavers Bartram as Surgeon Lieutenant is terminated, dated 28th February, 1959.

AUSTRALIAN MILITARY FORCES.

Citizen Military Forces.

Northern Command.

Royal Australian Army Medical Corps (Medical).—The provisional appointment of 1/39211 Captain J. J. Herron is terminated, 8th April, 1959. *To be Captain (provisionally), 9th April, 1959*—1/39211 John Joseph Herron.

Eastern Command.

Royal Australian Army Medical Corps (Medical).—To be Captain (provisionally), 16th April, 1959—2/127072 Tim John James Stewart.

Southern Command.

Central Command: Royal Australian Army Medical Corps (Medical).—To be Captain (provisionally), 21st April, 1959—4/32117 Michael Scollin Rice and 4/32120 Keith Mugford.

Reserve Citizen Military Forces.

Royal Australian Army Medical Corps (Medical).

Eastern Command.—To be Honorary Captain, 21st April, 1959—Keith Dudley Coulthurst.

Southern Command.—To be Honorary Major, 16th April, 1959—William John Stevenson. *To be Honorary Captains*—Graham Theodore Schmidt, 2nd March, 1959, Geoffrey Conron, 9th March, 1959, and Robert Graham Oliver, 16th March, 1959.—(Ex. Min. No. 60—Approved 19th May, 1959.)

ROYAL AUSTRALIAN AIR FORCE.

Active Citizen Air Force (Medical Branch).

The following officers are transferred to the Reserve:

No. 24 (City of Adelaide) Squadron.—Flight Lieutenant K. Tweedale (0211512) 14th March, 1955.

No. 25 (City of Perth) Squadron.—Flight Lieutenant B. R. Buttsworth (051361), 7th March, 1955; J. Sunderman (051378), 1st December, 1958.

Air Force Reserve (Medical Branch).

The following are appointed to a commission with the rank of Flight Lieutenant: Peter John Morris (257995), 1st January, 1959; Richard Allan Craven (268106), 1st March, 1959.

Air Cadet Andrew Slavin Luketina (040501) is provisionally appointed to a commission, 6th December, 1957, with the rank of Pilot Officer.

The provisional appointment of Pilot Officer J. F. MacDonald (035226) is confirmed and he is promoted to the rank of Flight Lieutenant, 1st March, 1959.

Squadron Leader A. H. Toyne (0312774) is promoted to the temporary rank of Wing Commander, 12th December, 1958.

The appointment of the following officers is terminated: Flight Lieutenants (Temporary Squadron Leaders) J. A. Horan (252570), S. D. Watsford (253263), N. Y. Youngman (277630), 1st March, 1959; Flight Lieutenants D. A. Noble

(015181), 4th January, 1959; P. H. Caldwell (0314261), J. T. Duhig (015104), R. H. Mackay (036622), R. J. Munroe (267510), 1st March, 1959; J. H. Smith (253338), 14th April, 1959; D. F. Burns (277557), 20th April, 1959.

The provisional appointment of Pilot Officer J. G. Downes (034795) is terminated, 1st March, 1959.

The following appointments, changes, etc., are published in the *Commonwealth of Australia Gazette*, No. 32, of May 28, 1959.

AUSTRALIAN MILITARY FORCES.

Regular Army Special Reserve.

Royal Australian Army Medical Corps (Medical)

To be Lieutenant, 9th February, 1959—QX700211 Leonard Cecil O'Brien.

Citizen Military Forces.

Northern Command.

Royal Australian Army Medical Corps (Medical).—1/39155 Captain B. H. Gutteridge ceases to be seconded whilst in the United Kingdom, 18th March, 1959. 5/26552 Captain (provisionally) R. F. Gorman relinquishes the provisional rank of Captain, 1st March, 1959, is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Northern Command), and is granted the honorary rank of Captain, 2nd March, 1959. 2/242959 Captain J. V. C. Brassil is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Northern Command), 18th March, 1959. *To be Captain (provisionally), 10th April, 1959*—1/39235 David Julius Cohen. *To be Temporary Major, 8th April, 1959*—1/39083 Captain R. Cantamessa.

Eastern Command.

Royal Australian Army Medical Corps (Medical).—The provisional rank of 2/79217 Captain R. W. Tinsley is confirmed. 2/127881 Major R. B. Geeves is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Eastern Command) 28th February, 1959. 6/15413 Captain (provisionally) W. H. Patterson relinquishes the provisional rank of Captain 1st March, 1959, is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Eastern Command), and is granted the honorary rank of Captain, 2nd March, 1959.

Southern Command.

Royal Australian Army Medical Corps (Medical).—To be Captain (provisionally), 10th April, 1959—3/147604 Brian Ainslie Minto.

Western Command.

Royal Australian Army Medical Corps (Medical).—5/26555 Captain (provisionally) F. W. S. Easton ceases to be seconded whilst in the United States of America, 6th April, 1959. 5/26555 Captain (provisionally) F. W. S. Easton relinquishes the provisional rank of Captain, 6th April, 1959, is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Western Command), and is granted the honorary rank of Captain, 7th April, 1959.

Notes and News.

New World Health Organization Area Representative for the South Pacific.

Dr. Lawrence O. Roberts, Tuberculosis Adviser of the World Health Organization (WHO), Western Pacific Regional Office, Manila, has been appointed Area Representative of the Organization for the South Pacific, with his office in Sydney, Australia. He will replace Dr. John Merril Cruikshank, who has resigned. The South-Pacific area includes Australia, New Zealand, Papua and New Guinea, Netherlands New Guinea and the Australian, French, New Zealand, United Kingdom and United States of America island territories in the South and West

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JUNE 20, 1959.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.[2]	Australian Capital Territory.	Australia.[2]
Acute Rheumatism	2(2)	2(1)	2	..	..	..	..	..	6
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	1	..	..	..	..	..	1
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	5(5)	23(23)	1(1)	..	..	..	..	..	29
Diphtheria	..	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	..	14(14)	..	3(3)	2(2)	..	..	..	19
Encephalitis	..	4	..	1	..	..	..	1	6
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	1	..	..	..	..	..	..	1
Infective Hepatitis	48(10)	25(10)	5(2)	7(6)	1	1(1)	..	..	87
Lead Poisoning	..	..	1(1)	..	..	..	..	..	1
Leprosy	..	..	..	..	2	..	..	..	2
Leptospirosis	..	1(1)	..	..	..	..	..	..	1
Malaria	..	..	1	..	..	..	..	..	1
Meningococcal Infection	1(1)	4(3)	2	1	..	2(2)	..	..	10
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	..	..	..	..	..	..	..	..
Puerperal Fever	..	..	7	..	..	..	..	..	7
Rubella	..	14(11)	..	2	4(4)	..	..	..	20
Salmonella Infection	..	..	..	..	1(1)	..	..	..	1
Scarlet Fever	6(4)	20(16)	2(1)	2(1)	2(2)	..	..	..	32
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1	..	..	..	..	..	1
Trachoma	..	..	..	..	16	..	..	..	16
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	22(15)	29(19)	28(17)	5(4)	7(3)	1	..	..	92
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

[2] Figures incomplete owing to absence of return from Northern Territory.

Pacific. As Area Representative, Dr. Roberts will represent Dr. I. C. Fang, Director of the WHO Western Pacific Regional Office, in the coordination of bilateral and multilateral health assistance programmes, and he will also represent Dr. Fang in negotiations with governments on technical and administrative questions in connexion with international health work.

Until his appointment with WHO in 1950, Dr. Roberts was principal medical officer of a British Government department. Before the war, he was resident medical officer of Papworth Village Settlement, Cambridge, England, and of the Royal National Sanatorium. Dr. Roberts obtained his medical qualification at St. Bartholomew's Hospital Medical College, London, in 1932, the M.R.C.P. in 1934, and M.D. (London) in 1936. His post-graduate public health degree was conferred at Harvard School of Public Health in 1955.

The WHO office in Sydney was established in June, 1956, with Dr. Cruikshank serving as the first Area Representative. Previously Dr. Cruikshank had been Inspector-General, South-Pacific Health Service, and Director of Medical Services, Fiji. Dr. Cruikshank was born in 1901 in Canada, and served from 1941 to 1946 as Hygiene Officer, Commonwealth Air Training Plan, Royal Canadian Air Force. He was Government Surgeon and Chief Medical Officer in the Bahamas (Colonial Medical Service) from 1928 to 1941. Dr. Cruikshank pursued his medical course at the McGill University, Montreal (Canada), from 1919 to 1925; he studied tropical medicine at the London School of Hygiene and Tropical Medicine, and obtained his post-graduate degree in public health from McGill University.

Royal Australasian College of Surgeons.

ADMISSION OF NEW FELLOWS.

THE following, having satisfied the Court of Examiners, were admitted to fellowship of the Royal Australasian College of Surgeons by the Council on June 20, 1959: Ronald Edward Aitken, Charles Francis Bellemore, James Murray Calvert, Gordon Joseph Clowes, Thomas Benjamin Comins, Donald Lochinvar Glen, David Campbell Glenn, Edmund John Hennessy, Colin Arthur Hobbs, Raymond Moulton Hollings, Donald William Hossack, Leslie Ernest Hughes, Alan Jessup, John Francis Lee, William Melville McDonald, Philomena McGrath, William David Proudman, Alastair Geoffrey Grindrod Robson, Joseph Patrick Savage, Norman Reginald Scott-Young, Harry Segal, Ngoh Chuan Tan, Cedric Francis Thwaites, David Gerard Walker, Robin Charles Winfield Williams, John Saxon Wright.

FACULTY OF ANÆSTHETISTS.

Admission of New Fellows.

THE following, having satisfied the Court of Examiners, were admitted to fellowship of the Faculty of Anæsthetists, Royal Australasian College of Surgeons, by the Council on June 20, 1959: William Moncrieff Crosby, Graham Chudleigh Fisk, Vera Gallagher, Gordon Alfred Harrison, Ross Beresford Holland.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Hussain, Mohammed Yusuff, M.B., B.S., 1958 (Univ. Sydney), Ryde District Soldiers' Memorial Hospital, Ryde.

The undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Gilles, Samuel, M.B., Ch.B., 1944 (Univ. Liverpool), Morris Hospital, Northfield.

Valente, Leonard Joseph, qualified M.B., B.S., 1957 (Univ. Adelaide), 15 Connor Street, Glanville.

Thompson, Bryan William, qualified M.B., B.S., 1957 (Univ. Adelaide), Cleve.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association: Ryan, Gerald Anthony, qualified M.B., B.S., 1958; Eadie, Norman Basil Menzies, L.R.C.P. et S., Edinburgh, 1926, D.L.O., F.R.A.C.S.; Yates, Lawrence Anthony, M.B., B.S., 1956 (Univ. Adelaide).

Deaths.

THE following death has been announced:

SIGLIN.—Max Siglin, on July 10, 1959, at Broome, Western Australia.

Diary for the Month.

JULY 28.—New South Wales Branch, B.M.A.: Hospitals Committee.
JULY 30.—Western Australian Branch, B.M.A.: General Meeting.
JULY 30.—South Australian Branch, B.M.A.: Scientific Meeting.
JULY 30.—New South Wales Branch, B.M.A.: Branch Meeting.
AUGUST 4.—New South Wales Branch, B.M.A.: Organization and Science Committee.
AUGUST 5.—Victorian Branch, B.M.A.: Branch Meeting.
AUGUST 5.—Western Australian Branch, B.M.A.: Branch Council.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales. Anti-Tuberculosis Association of New South Wales.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2-3.)

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